

Indian J. Chem., Vol. 25B No. 1 pp. 1-112

January 1986

CODEN: IJOCAP ISSN: 0019-5103

25B(1) 1-112 (1986)

# INDIAN JOURNAL OF CHEMISTRY

SECTION B

(Organic including Medicinal)

99  
5/5/86  
Smt



Published by

PUBLICATIONS & INFORMATION DIRECTORATE (CSIR), NEW DELHI

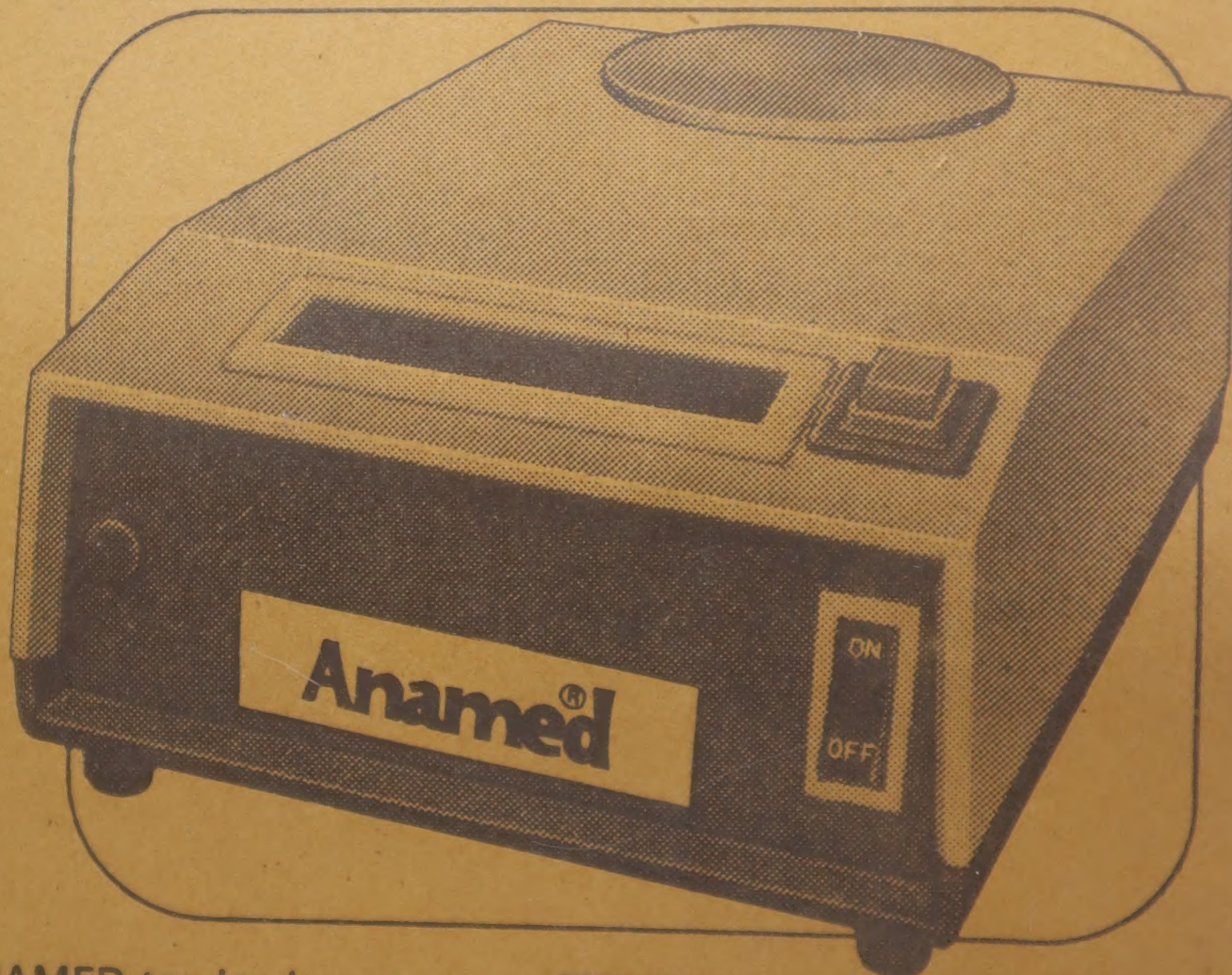
in association with

THE INDIAN NATIONAL SCIENCE ACADEMY, NEW DELHI

# Precision and fast weighing, a problem?

You need an Electronic Top Loader for your lab.

ANAMED offers you a wide range of instant weighing top loaders from sensitivities 0.001 gm to 0.1 gm.



ANAMED top loaders are now widely sold and well accepted. Please ask for a copy of the literature and the price List today. Specify Model Number when you ask for a quotation.

MODELS	CAPACITY	SENSITIVITY
M-50	50 gm.	0.001 gm.
M-200	200 gm.	0.01 gm.
M-300	300 gm.	0.01 gm.
M-300 DR	300/30 gm.	0.01/0.001gm.
M-3000	3000 gm.	0.1 gm.
M-3000 DR	3000/300gm.	0.1/0.01 gm.

*Write to us or visit us today.*

**ANAMED INSTRUMENTS PVT. LTD.**

10 A, Majithia Industrial Estate, Deonar, Bombay 400 088.

Phone: 5516908 • Telex: 6804.

# INDIAN JOURNAL OF CHEMISTRY

## Section B: Organic Chemistry including Medicinal Chemistry

### Editorial Board

Prof. (Mrs) Asima Chatterjee  
Department of Chemistry  
Calcutta University  
Calcutta 700 009

Dr Sukh Dev  
Multi-Chem Research Centre  
Nandesari 391 340

Dr Nitya Anand  
Central Drug Research Institute  
Lucknow 226 001

Prof. S Swaminathan  
Department of Chemistry  
University of Madras  
Madras 600 025

Prof. S V Kessar  
Department of Chemistry  
Panjab University  
Chandigarh 160 014

Prof. G S R Subba Rao  
Department of Organic Chemistry  
Indian Institute of Science  
Bangalore 560 012

Prof. Goverdhan Mehta  
School of Chemistry  
University of Hyderabad  
Hyderabad 500 134

Prof. U R Ghatak  
Indian Association for the  
Cultivation of Science  
Calcutta 700 032

Prof. Harjit Singh  
Department of Chemistry  
Guru Nanak Dev University  
Amritsar 143 005

Dr A V Rama Rao  
Division of Natural Products  
National Chemical Laboratory  
Pune 411 008

Dr. Girjesh Govil  
Tata Institute of Fundamental Research  
Homi Bhabha Road  
Bombay 400 005

Prof. S Ranganathan  
Department of Chemistry  
Indian Institute of Technology  
Kanpur 208 016

Prof. P Balaram  
Molecular Biophysics Unit  
Indian Institute of Science  
Bangalore 560 012

Sh. S P Ambasta, Editor-in-Chief  
*Ex-officio*

---

**Editor-in-Charge: S.S.Saksena**

**Editors: S.A.I. Rizvi and L.M. Mathur**

**Asstt Editor: S. Hotchandani**

---

**Published by the Publications & Information Directorate (CSIR), Hillside Road, New Delhi 110 012**

**Editor-in-Chief: S.P. Ambasta**

---

© Copyright, 1986, by the Council of Scientific & Industrial Research, New Delhi 110 012

The Indian Journal of Chemistry is issued monthly in two sections: A and B. Communications regarding contributions for publication in the journal should be addressed to the Editor, Indian Journal of Chemistry, Publications & Information Directorate, Hillside Road, New Delhi 110 012.

Correspondence regarding subscriptions and advertisements should be addressed to the Manager, Sales & Advertisement, Publications & Information Directorate, Hillside Road, New Delhi 110 012.

The Publications & Information Directorate (CSIR) assumes no responsibility for the statements and opinions advanced by contributors. The Editorial Board in its work of examining papers received for publication is assisted, in an honorary capacity by a large number of distinguished scientists, working in various parts of India.

Annual Subscription: Rs. 160.00 £ 30.00 \$ 53.00; 50% discount admissible to research workers and students and 25% discount to non-research individuals on annual subscriptions.

Single Copy: Rs. 16.00 £ 3.00 \$ 5.30

Payments in respect of subscriptions and advertisements may be sent by cheque, bank draft, money order or postal order marked payable to Publications & Information Directorate, Hillside Road, New Delhi 110 012.

Claims for missing numbers will be allowed only if received within 3 months of the date of issue of the journal plus the time normally required for postal delivery of the journal and the claim.

## Author Index

Aboo Shoeb	66	Maiti Swaraj B	15
Ahluwalia V K	51	Majumdar K C	56
Anand Nitya	72	Mehta R K S	60, 111
		Mitra R B	92
		Muljiani Z	92
Beltrão Thereza Maia	63		
Bhagat Ram	76	Narasimhan N S	12
Bhanu Chanda	9	Narayana V Lakshmi	76
Bhide M B	102	Nayak U R	22,28,32,36,40
Borate H B	9	Nielsen Lawrence T	63
Chari V Mohan	100	Padhye A M	92
Chatterjee Amareshwar	15	Paramasivam R	89
Chattopadhyay S	56	Paraskar Sunil R	102
Cherniak Robert	85		
Deepak Desh	44	Raju K Raghava	94,97
Deshpande S R	92	Raju G V Subba	100
Desiraju Gautam R	1	Ramakrishnan V T	89
Devi P Aruna	100	Rama Rao A V	9
Dhavale D D	12	Rao A S	46
		Rao Ch Bheemasankara	100
Gupta Manisha	9	Rao P S	94,97
Gupta Ranjna	51	Rastogi Shri Nivas	106
		Raychaudhuri S R	15
Hari M I	83	Sarin Rakesh	81
Jain A C	88	Satyanarayana N	22,28,32
Jalisatgi S S	83	Sen B K	56
Jayachandran T	89	Sengupta Dibyendu	72,85
Joshi Vidya	83	Shankaran K	46
		Shitole H R	36
Khan Khalid A	66	Shridhar D R	76
Khanna Vijay	102	Singh Harjit	81
Khare Anakshi	44	Srivastava Rajendra Mohan	63
Khare Maheshwari P	44	Surat Kumar	106
Krishna P Gopala	100		
Krishna R R	76	Talekar D G	46
Kundu A P	15	Tyagi O D	88
Ladwa P H	102		
Madhusudanan K P	66	Vaidya A S	46
		Vaidya S P	36,40

# Indian Journal of Chemistry

Sect. B: Organic Chemistry, including Medicinal Chemistry

VOL. 25B

NUMBER 1

JANUARY 1986

## CONTENTS

### Advances in Contemporary Research

- Some Chemical Implications of Database Derived Crystallographic Information ... 1  
Gautam R Desiraju

### Papers

- Asymmetric Synthesis of *R*-(–)-2-Acetyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene—  
A Key Synthon for Synthesis of 11-Deoxyanthracyclinones ... 9  
A V Rama Rao\*, Bhanu Chanda, H B Borate & Manisha Gupta
- Synthesis of 6-Methyl-11-demethylellipticine ... 12  
N S Narasimhan\* & D D Dhavale
- A New Total Synthesis of C-20 Functionalised Ring-C Aromatic 18-Norsteroid ... 15  
Swaraj B Maiti, A P Kundu, Amareshwar Chatterjee & S R Raychaudhuri\*
- Base-induced Thermal Decomposition of Terpenoid Tosylhydrazones: Part I – Chemistry of  
Diazolongibornanes ... 22  
N Satyanarayana & U R Nayak\*
- Base-induced Thermal Decomposition of Terpenoid Tosylhydrazones: Part II – Chemistry of  
8-Diazoisolongifolane/9-Diazoisolongifolene ... 28  
N Satyanarayana & U R Nayak\*
- Base-induced Thermal Decomposition of Terpenoid Tosylhydrazones: Part III – Chemistry of  
12-Diazoallosolongifolane/12-Methyl-12-diazoallosolongifolane ... 32  
N Satyanarayana & U R Nayak\*
- Longihomocamphenilane-7,8-dione: Reactivity of Carbonyl Groups via Monofunctional  
Derivatives of the Diketone ... 36  
S P Vaidya, H R Shitole & U R Nayak\*
- 9-Methylenelongibornane: Lewis Acid-induced Transannular Hydride Shift/Rearrangement to  
9-Methylisolongifolene/7-Isopropyl-1,1,3-trimethyltetralin ... 40  
S P Vaidya & U R Nayak\*
- A New Pregnane Glycoside from *Periploca calophylla* ... 44  
Desh Deepak, Maheshwari P Khare & Anakshi Khare\*
- Synthesis of (1*RS*, 7*SR*, 8*a RS*)-1,2,3,5,6,7,8,8*a*-Octahydro-4,7-dimethyl-1-naphthoic Acid & Its  
Reaction with Lead Tetraacetate ... 46  
K Shankaran, D G Talekar, A S Vaidya & A S Rao\*
- Acid-catalysed Condensation of Isoprene with  $\beta$ -Orcinaldehyde: Synthesis of 2,2-  
Dimethylformylchromans & Synthesis of 5-Methylxanthyletin & Seselin Derivatives 51  
V K Ahluwalia\* & Ranjna Gupta

Continued overleaf

# CONTENTS

Synthesis of Bicyclic Oxygen Heterocycles: Part II – Synthesis of 9-Aryloxy-3-bromo-2,4-ethanochromans ... ..	56
S Chattopadhyay, B K Sen & K C Majumdar*	
Chemistry of Carbenes: Part III – Reaction of Methylene with Ethyl <i>n</i> -Propyl Ether ...	60
R K S Mehta	
Mass Spectra of Benzamidoxime & Its O-Methyl Derivative ... ..	63
Rajendra Mohan Srivastava* & Thereza Maia Beltrão & Lawrence T Nielsen	
Chemical Ionization Mass Spectra of 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octanes ...	66
K P Madhusudanan*, Khalid A Khan & Aboo Shoeb	
Synthesis of Pyrido[4,3- <i>b</i> ]dibenzofuran, Pyrido[4,3- <i>b</i> ]phenoxathiin, 6-Ethylpyrido[4,3- <i>b</i> ]phenothiazine & Related Compounds as Ellipticine Analogs ... ..	72
Dibyendu Sengupta & Nitya Anand*	
Synthesis & Antibacterial Activity of 2-(1-Ethyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-alkoxyiminoacetic Acids & Their Esters ... ..	76
D R Shridhar*, Bhagat Ram, R R Krishna & V Lakshmi Narayana	
<b>Notes</b>	
Heterocyclic Ring Interchange Reactions ... ..	81
Harjit Singh* & Rakesh Sarin	
Studies in Hydrazone Rearrangement: Synthesis of Anilides.. ... ..	83
Vidya Joshi*, S S Jalisatgi & M I Hari	
Structural Analogs of 2-Keto-3-deoxy-D-mannooctulosonic Acid ... ..	85
Dibyendu Sengupta* & Robert Cherniak	
Synthesis of Xambioona, a Bispyranoflavanone ... ..	88
A C Jain* & O D Tyagi	
Synthesis of Condensed Carbostyrils ... ..	89
T Jayachandran, R Paramasivam & V T Ramakrishnan*	
Regiochemistry of Alkylation in Substituted 1,2,4-Triazoles... ..	92
R B Mitra*, Z Muljiani, A M Padhye & S R Deshpande	
Chemistry of Lichen Products: Part V – Synthesis & Antimicrobial Activity of Some New 1,4-Benzoxazinones from Pulvinic Acid Dilactone ... ..	94
K Raghava Raju & P S Rao*	
Chemistry of Lichen Products: Part VI – Synthesis of Some New Benzimidazole Derivatives from Pulvinic Acid Lactone & Their Fungicidal Activity ... ..	97
K Raghava Raju & P S Rao*	
Chemical Examination of <i>Premna</i> Species: Part XI – Structure of Premnoside-A from <i>Premna latifolia</i> Roxb. (var <i>cuneata</i> ) .. ... ..	100
Ch Bheemasankara Rao*, P Gopala Krishna, P Aruna Devi, G V Subba Raju & V Mohan Chari	
Addition of 4-Hydroxycoumarin to $\alpha,\beta$ -Unsaturated Carbonyl Derivatives & Mannich Base Methiodides Derived from Cyclic Ketones ... ..	102
Vijay Khanna, Sunil R Paraskar, P H Ladwa* & M B Bhide	
<i>p</i> -(Cyclopentenyl)phenol Derivatives as Potential Biodynamic Agents ... ..	106
Surat Kumar & Shri Nivas Rastogi*	
Chemistry of Carbenes: Part II – Reaction of Methylene with Dimethyl Ether ... ..	111
R K S Mehta	

## Some Chemical Implications of Database Derived Crystallographic Information†

GAUTAM R DESIRAJU

School of Chemistry, University of Hyderabad, P.O. Central University, Hyderabad 500 134

Received 4 November 1985

X-ray crystallography is one of the most powerful methods for studying molecular structures. Although our country has witnessed many advances in the theory and practice of crystallography, Indian organic chemists have by and large generally not recognised the power and applicability of this technique. The major concern in any X-ray structure determination is the so-called 'phase problem'. Put simply, the diffraction intensities, which are the measured quantities, cannot be related directly to the electron density (i.e., the crystal structure) since some additional information known as the 'phase angle' is lost in the intrinsic nature of the diffraction experiment. The whole science and art of X-ray crystallography consists then of the various ways in which this 'phase angle' may be determined so that the problem is reduced to the mathematical operation of a Fourier Transform which relates the 'intensity-cum-phase' information to the electron density<sup>1-3</sup>.

The earliest organic crystal structures to be determined (1925-1940) were those of very simple molecules. The solution of the hexachlorobenzene structure by Lonsdale and of *p*-benzoquinone and the polymorphs of resorcinol by Robertson are now part of crystallographic history. These structural analyses (in other words, the solution of the phase problem) were only possible because of some simplifying features in either the molecular structure itself or in the packing; these simplifying features were exploited to yield special methods, almost unique to each structure. The structure determination became then, a study in itself, with the crystallographer required to have a specialised and intimate knowledge of the peculiarities of each structure<sup>2</sup>.

By 1940 the stage was set for major advances in the theory of X-ray crystallography. Very rapidly, the 'heavy-atom' or Patterson technique and those of 'isomorphous replacement' and 'anomalous scattering' came upon the scene with the result that by the

mid-fifties major molecules like Vitamin B<sub>12</sub> were being attempted and solved by Hodgkin and others.

Independently, new and different strategies for solving the phase problem, using statistics and inequalities, made their appearance. These are familiarly known to crystallographers as 'Direct Methods' and through the work of Hauptmann, Karle, Sayre and Woolfson it soon became apparent that these new methods were very powerful indeed. No longer did one require a 'heavy atom' in a crystal, nor was there need of some crystallochemical trick which alone could be exploited to solve a particular structure. Any molecule could, in principle, be solved provided crystals were available<sup>3</sup>.

The example of the Vitamin B<sub>12</sub> structure was particularly valuable for organic chemists since it clearly conveyed the message that, as a structure determining procedure, crystallography was by far swifter, more economical and unambiguous than the earlier degradative methods. Many organic chemists started collaborating with crystallographers on structure elucidation work. It was during the sixties that the number of crystal structures solved per year rose sharply and the rate at which this number grew from year to year also started increasing. For instance, while 3971 structures were reported between 1960 and 1969, this figure rose sharply to 21729 during the next decade. So rapid have been the advances in digital technology, that the structure determination of small organic molecules (less than 30-40 non-hydrogen atoms) has become almost fully automated. The result is that there are now about 50000 organic and organometallic crystal structures solved and that this number is projected to exceed 75000 by 1990.

### Nature and Growth of Crystallographic Information

Although chemists started using crystallography in the sixties, they were often interested in little more than the atomic connectivity within the molecule. In almost all cases crystallography was used to clarify matters such as the position and stereochemistry of a

† Based on the Cambridge Structural Database.

substituent, the size of a ring or some such molecular attribute. Correlations of intramolecular bond lengths and angles in related structures were reported by crystallographers, but these were by no means exhaustive nor were they, in many cases, presented in ways meaningful to chemists. Information concerning intermolecular geometry and molecular packing was even sparser<sup>4</sup>. Such discussions were avoided by chemists and crystallographers alike and there was much scepticism about their relevance to molecular properties in solution.

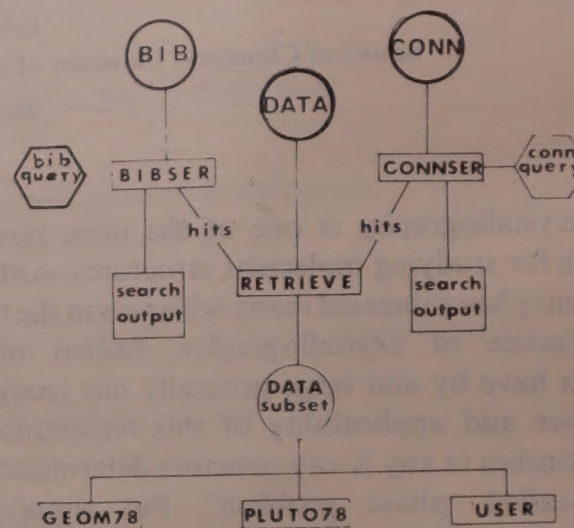
The numerical nature of crystallographic results makes them particularly suited to storage and retrieval in a modern computer system. The growth of machine-readable data-bases grew out of earlier manual compilations and four structural databases are of relevance to chemists today. These cover respectively organics, organometallics and metal complexes (Cambridge Structural Database), inorganics and minerals (Inorganic Crystal Structure Database, Bonn), metals and alloys (Metals Data File, Ottawa) and proteins (Protein Data Bank, Brookhaven). The Cambridge Structural Database (CSD) contains bibliographic and numerical results for full 3D-X-ray and neutron studies of organics, organometallics and metal complexes<sup>5</sup>. The CSD includes all structures published or deposited since 1935, contains information on 50000 structures to date and is currently increasing at the rate of 5000 structures per year. It is worth stressing that out of a total of 49150 structures in the CSD till mid-1984, some 22838 structures, i.e. nearly 50%, result from work done after 1980. The availability of modern diffractometers in recent years has meant that the precision of these structures is quite good. While the mean R-factor for a structure was 0.106 in the period 1960-69, this number has fallen to 0.057 for the period 1980-84. The proportion of organometallic structures to total structures is also increasing rapidly reflecting the growing importance of these compounds in modern chemistry. For instance, out of the 3971 structures reported between 1960-69, 1238 (or 31%) are organometallic compounds. For the period 1980-84, however, the percentage of organometallic structures has risen as high as 43% with 9689 reported structures out of the total of 22838. In fact, it is possible that the development of this area has been largely due to the ready availability of crystallography to characterise these compounds exactly, a task difficult to perform by any other technique.

This body of information in the CSD is being updated continuously. Copies of the CSD are sent periodically to several centres and in India this information is received and handled by the National Information Centre for Crystallography, Department

of Crystallography and Biophysics, University of Madras. The bibliographic information is also available in book form<sup>6</sup>.

### Organisation of the Cambridge Structural Database

A flow chart of the CSD is shown in Figure 1. The



heart of the system are the two main search programmes BIBSER (bibliographic search) and CONNSER (connectivity search). Using the bib query, BIBSER locates entries in the file BIB on the basis of chemical name, molecular formula, chemical class, author, journal name etc. CONNSER on the other hand, is used to search for compounds containing specific chemical fragments. In each case, a bibliographic listing constitutes the search output. For each query, a file of reference codes is also produced (hits) and this file may be used to RETRIEVE numerical data for these structures. The reference code is a six-letter (plus occasional numerical) code which uniquely determines a particular entry in the CSD. The numerical data retrieved may be used to calculate intra- and intermolecular geometries (GEOM 78) or to make plots and diagrams of the molecular and crystal structure (PLUTO 78)<sup>7</sup>.

### Some Applications of the CSD

The most interesting aspect of database information is that although it exists only because of the activity of crystallographers, potential for its greatest use is among organic chemists and that no specialised knowledge of crystallography is required for its use and interpretation. Structural information can be used in various ways and a few of the more important ones are: (A) Studies of intramolecular geometry; mean geometries; substituent and hybridisation effects; conformational analysis. (B) Inference of reaction pathways; ground state structure and chemical reactivity. (C) Studies of intermolecular geometry;

hydrogen bonding; crystal structure systematics; long range contacts.

All these topics have been well reviewed<sup>8,9</sup>. The brief description which follows is not exhaustive and more detailed accounts are given in some of the references at the end of this article.

#### (A) Intramolecular geometry

Since the database consists of atomic co-ordinates, information concerning intramolecular geometry may be readily derived from the retrieved data. Originally, detailed discussions of the geometry of individual molecules were described by the investigating crystallographers themselves. Now, it is possible to retrieve whole groups of structures and determine the mean geometries of complete chemical residues. These find use in model building, theoretical studies and in the study of phenomena such as tautomerism and hydrogen bonding<sup>8</sup>.

A very large number of studies concerning substituent and hybridisation effects have been reported<sup>8</sup>. For example, it has been found that the regular hexagonal geometry of benzene is perturbed when the ring is substituted by strong electron-withdrawing or donating groups. The changes in the bond lengths and angles systematically relate to quantities such as the Taft inductive and resonance parameters<sup>10</sup>. Examination of molecular geometries of a large number of cyclopropane derivative shows the effects of conjugation of the cyclopropyl group with  $\pi$ -acceptor substituents<sup>11</sup>. The importance of the CSD in such studies is that a large number of compounds may be simultaneously correlated. Structural patterns can be easily detected and a stray observation (outlier) distinguished from a systematic trend.

An interesting example as to how rates of condensation of benzaldehyde with a series of ketosteroids may be correlated with the conformation of the steroid rings has been described<sup>8</sup>. Other reviews of conformational analysis in steroids, alkaloids and terpenes show the importance of crystallographic data in such problems<sup>8</sup>.

#### (B) Inference of reaction pathways

The use of crystallographic information for this purpose is illustrated by the familiar example of the addition of a nitrogen nucleophile to carbonyl carbon<sup>2,8,9</sup>.  $N \dots C=O$  contacts in six crystal

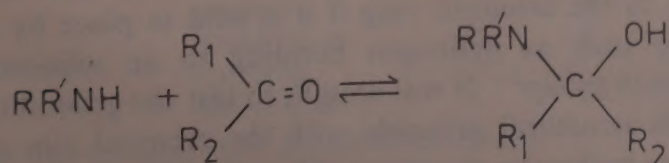
structures were examined, the  $N \dots C$  distances ranging from 2.91 Å (non-bonded  $N \dots C=O$ ) to 1.49 Å (covalent  $N-C-O$ ). An important assumption is that each NCO contact in each of these six structures is a good approximation to the point on or near the minimum energy pathway followed by the nitrogen nucleophile as it approaches the carbonyl group. While the longest contact represents the incipient addition reaction, the shortest contact corresponds to the completed reaction. Between them, the four other contacts should map out the minimum energy reaction pathway with each structure providing a picture of the NCO fragement in a particular environment which is not too far from the reaction coordinate. In this particular example, the  $N \dots C=O$  geometries were tabulated and it was seen that the  $N \dots C$  distance correlates inversely with the  $C=O$  distance and with the deviation of carbonyl carbon from the  $R_1R_2O$  plane (i.e., trigonal to tetrahedral geometry with the progress of the reaction). This structure correlation method of Dunitz and Bürgi has not only been used by these authors but by others in describing many cases of bond-breaking and making<sup>12-14</sup> and an important extension of this method to the cleavage of ethers has been reported recently by Allen and Kirby<sup>15</sup>.

#### (C) Intermolecular geometry

Since geometrical calculations may be performed readily using the CSD, several interesting studies have been carried out to show that molecules with certain functional groups tend to be mutually oriented in the crystal in only certain ways. This specificity of intermolecular geometry is manifested in a large number of effects such as hydrogen bonding, donor-acceptor interactions, halogen-halogen and sulphur-sulphur contacts.<sup>16</sup>

The study of hydrogen bonding for instance, is of great importance to chemists, crystallographers and molecular biologists alike. Several very detailed studies of this phenomenon have appeared since the CSD became available<sup>17-20</sup>. In particular, one may note the occurrence in several crystal structures of short  $C-H \dots O$  non-bonded contacts that are in the nature of hydrogen bonds. So specific are the geometries of these contacts for a particular type of oxygen (ketone, ether etc.) that there seems to be no doubt that these very specific albeit weak contacts may be referred to as  $C-H \dots O$  hydrogen bonds.

Examination of intermolecular geometries is likely to be important in at least two other areas. The prediction of crystal structures of molecular solids is a science still in its infancy and is fraught with several problems since the stable crystal structure of an organic compound is a result of a balancing of a large number of (usually) improperly understood interactions<sup>4</sup>. Rather than



attempting to grapple with the nature of these weak forces, approaches through the CSD may be more fruitful since, in many cases, the presence of the same weak intermolecular interaction results in the same geometrical motif or pattern of molecules in the crystal<sup>16</sup>. Several structures are controlled by relatively weak interactions of the C—H...O, Cl...Cl, S...S, C—H...N, or C...Cl type and a valuable insight into the consequences of these interactions, if not their nature, may be obtained by examining an entire family of structures with the CSD. For example, many planar chloro-aromatic compounds adopt a crystallographic short axis of approximately 4 Å and this results from the presence of a large number of 'in-plane' Cl...Cl contacts which may be significantly shorter than the van der Waals distance of 3.6 Å. A retrieval of all such compounds and further intermolecular geometrical calculations may be performed readily with the CSD<sup>21, 22</sup>.

The other application of the study of intermolecular geometry in crystals is to the issue of conformational processes in solution. The long-standing objection of solution chemists to the relevance of crystallographically derived information to such processes, was not really well-answered till the advent of the Database. Parthasarathy and co-workers derived all possible nucleophilic and electrophilic contacts to divalent sulphur and deduced that while electrophiles approach perpendicular to the  $R_1R_2S$  plane, nucleophiles approach along the  $R_1R_2S$  plane at an angle of about  $180^\circ$  to one of the S—R bonds<sup>23</sup>. These preferences were found for contacts which were well beyond what could be considered a "short non-bonded contact". Similar trends have been seen for groups approaching oxygen, fluorine and other atoms<sup>16</sup>. The striking features in all these cases are the narrow ranges of intermolecular geometries, the large number of structures (hundreds) where these geometries are found and the very weak nature of the contacts (long intermolecular distances). All this suggests that when data from many structures are examined, even relatively long contacts may have to be considered seriously. These patterns of molecules in the crystal may perhaps represent ways in which molecules approach each other in solution, prior to chemical reactions.

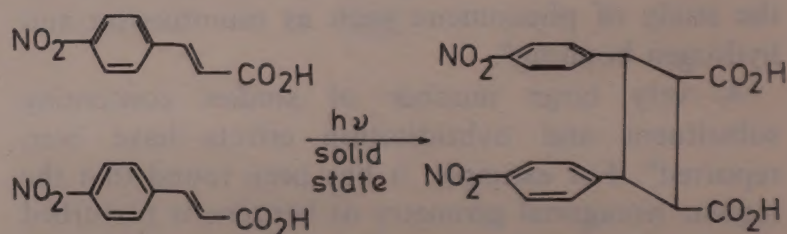
### Examples

#### (A) Hydrogen bonding in nitroalcohols and nitrophenols

A typical application of the CSD to an organic chemical problem is illustrated by the following example where the presence or lack of hydrogen bonding is expected to modify solid state photoreactivity. The CSD has been used to retrieve co-

ordinates for relevant structures and subsequent geometrical calculations are then performed.

It was observed that several nitro-substituted cinnamic acids and styrenes exhibited anomalous photostability when irradiated in the solid state even though 'potentially reactive' double bonds are within 4 Å of each other in the crystal structure<sup>24, 25</sup>. Such photostable compounds include 2,4-dinitrocinnamic acid, 3,4-methylenedioxy-6-nitrocinnamic acid, *cis*- $\beta$ -nitrostyrene and the 1:1 donor-acceptor complexes of 2,4-dinitrocinnamic acid with respectively, 3,4-dimethoxy-3,4-dihydroxy- and 3-methoxy-4-hydroxy-cinnamic acids. On the other hand it has been reported that the three nitrocinnamic acids undergo solid state photodimerisation (yields of cyclobutane, *para* > *meta* > *ortho*).<sup>26</sup>



An obvious structural difference between the reactive nitrocinnamic acids and the photostable nitroaromatics mentioned above is that all the inert compounds have at least one nitro group that is *ortho* to a  $-\text{CH}=\text{}$  group and which therefore cannot be coplanar with the aromatic ring. Now, the crystal structures of the nitrocinnamic acids are unknown but it is reasonable to assume a higher degree of nitro group coplanarity with the aromatic ring for the *meta* and *para* acids (60%, 70% dimer yields) as compared to the *ortho*-isomer (27% dimer yield) where coplanarity is impossible. In addition, one may note that there is no intramolecular steric hindrance to the nitro group being coplanar with the conjugated system in photoreactive crystalline *trans*- $\beta$ -nitrostyrene (crystal structure also unknown) while the nitro group is almost certainly out of the aromatic ring plane in the isomeric *cis*- $\beta$ -nitrostyrene which does not dimerise in the solid state. All these observations suggest that if the nitro group were parallel to the aromatic ring in a cinnamic acid or a styrene, topochemical photodimerisation would take place if permitted by the crystal structure.

Now, it has also been reported that for nitro aromatics, the nitro group is constrained to be in the plane of the aromatic ring if it is held in place by a device such as hydrogen bonding to an adjacent hydroxyl group<sup>27</sup>. It was sought to test the generality of this structural principle with the eventual aim of linking molecular planarity with solid state reactivity.

Accordingly a connectivity search was performed on the CSD (1982 version) to yield 51 compounds containing the  $(\text{HO})-\text{C}-\text{C}-(\text{NO}_2)$  fragment. In 14 compounds this group was part of an aliphatic residue while the 37 others were various types of substituted *ortho*-nitrophenols. Pertinent geometrical calculations on some of these compounds are presented in Tables 1 and 2. These calculations, performed with GEOM78, indicate the deviations from planarity of the nitro group and the strength of the intramolecular  $\text{O}-\text{H}\cdots\text{O}$  hydrogen bond. Table 1 shows that among the 37 aromatic compounds there is a clear trend for the nitro group *ortho* to a hydroxyl group to be strongly intramolecularly hydrogen bonded to the latter, with the mean  $\text{O}\cdots\text{O}$  distance being 2.58 Å. As a consequence, such a nitro group will be coplanar with the aromatic ring. Some typical compounds are 2-nitrophenol (ONITPH); 4-chloro-2-nitrophenol (NTCPOL) and 2,4-dinitrophenol (DNOPHL). For compounds like picric acid

(PICRAC) where two nitro groups flank the hydroxyl group, only one of them as expected, is observed to be coplanar and hydrogen bonded.

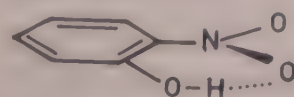


Table 2 lists the corresponding intramolecular geometrical details for some of the aliphatic hydroxy nitro compounds. In contrast to the nitrophenols described above, there does not seem to be any significant intramolecular hydrogen bonding in these  $\alpha$ -nitroalcohols and the conformational flexibility permitted in these systems seems to preclude planar arrangements of the  $\text{HO}-\text{C}-\text{C}-\text{NO}_2$  fragment.

One of the 37 aromatic compounds identified in the CSD connectivity search is methyl 3-nitro-4-hydroxy-*trans*-cinnamate (1), MHNTCN, and it is of relevance to the solid state reactivity problem discussed above. In the crystal structure of ester 1,

Table 1—Some Intramolecular Geometrical Details for Substituted *ortho*-Nitrophenols<sup>a,b,c</sup>

‡ = Torsion angle 1, 2, 4, 5  
 $\Omega$  = Angle between planes (1234) and (2456)  
D = O3...O6

Refcode	$\tau^\circ$	$\Omega^\circ$	D(Å)	Refcode	$\tau^\circ$	$\Omega^\circ$	D(Å)
ANTPIC	4	3	2.55	BAKLII	7	173	2.5
BCRNSY	-165	13	2.61	BDNPOL	-9	171	2.60
CBCPIC	-4	2	2.58	CDNPOL	-5	6	2.59
CLETNP	4	3	2.56	CLETNP	-6	172	2.61
CLNODL	-7	6	2.56	CLVINA	0	1	2.56
CLVINB	15	164	2.57	CLVINB	4	4	2.56
DNLTyr10	-159	23	2.66	DNOPHL	3	2	2.59
DNOPHLO1	2	3	2.61	DNPHOL	13	165	2.57
DNPHOL	177	1	2.58	ETycNP	3	4	2.57
ETycNP	177	2	2.56	IPycNP	0	1	2.55
MHNTCN	174	5	2.60	NBARBA	-5	4	2.50
NIOPH	4	3	2.56	NTCPOL	0	0	2.61
NTCPOL	0	0	2.59	ONITPH	1	1	2.59
PICRAC	-7	8	2.55	PICRAC	0	0	2.55
PICRAC11	8	-170	2.58	PICRAC11	-3	2	2.59
SNITYR10	-178	7	2.64	SNITYR10	176	5	2.63

(a) The names of the compounds may be retrieved by using the REFCODE. A complete list is available from the author on request.

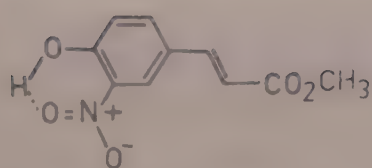
(b) All angles corrected to the nearest degree.

(c) For picric acid, two structure determinations on the same modification exist (PICRAC and PICRAC11). There are two molecules in the asymmetric unit ( $\text{PCa}_2$ ,  $Z=8$ ) and the data above refer only to the nitro group which is hydrogen bonded to the hydroxyl group.

Table 2—Some Intramolecular Geometrical Details for  $\alpha$ -Nitroalcohols<sup>a</sup>

Refcode	$\tau^\circ$	$\Omega^\circ$	D(Å)	Refcode	$\tau^\circ$	$\Omega^\circ$	D(Å)
BAKNUW	67	104	2.87	BHNCHX	-131	108	2.94
BRNOHA	-85	71	2.88	BRNOHB	-51	159	3.15
BROHXN	97	108	2.89	DETND	40	70	2.97
HNAFPY10	62	81	3.29	BMXHNO	-118	86	3.17
MENPDL	-60	93	3.15	NINTHT	167	57	2.96
NMALAM	2	2	4.04	OHNODC	115	62	3.75

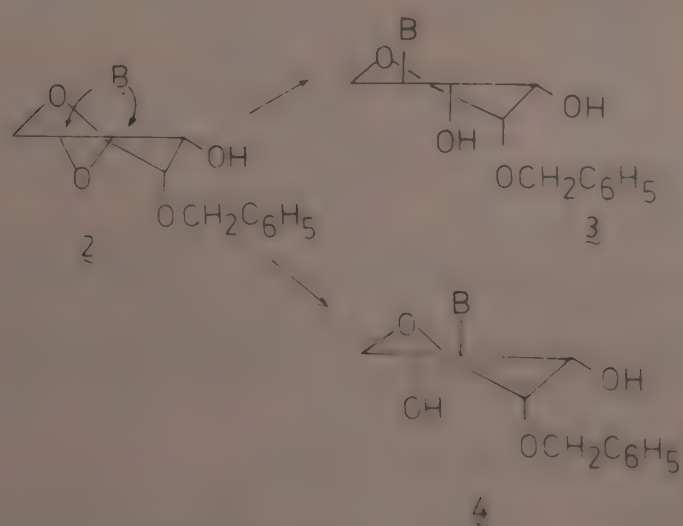
(a) For an explanation of symbols see Table 1.



molecules are planar and the O...O (nitro to hydroxyl) distance is 2.59 Å. Further, the short crystallographic axis (also retrieved from the CSD) is 3.873 Å which means that the compound is expected to form a mirror symmetric cyclobutane upon topochemical dimerisation. Ester 1 was therefore judged to be an ideal model compound and its behaviour upon solid state irradiation was examined. Yet, it too was completely unaffected indicating that coplanarity, or the lack of it, of the nitro group may not be the crucial factor in determining the ease of topochemical photodimerisation in these cases. More mechanistic details of these reactions are presented elsewhere<sup>25</sup> but here it is sought to emphasise that the CSD may be used to conveniently and rapidly test a structural conjecture. Identification of the methyl ester 1 as a good model compound is, in principle, possible using conventional library methods but it would have been an arduous task. With the CSD, the process becomes much easier.

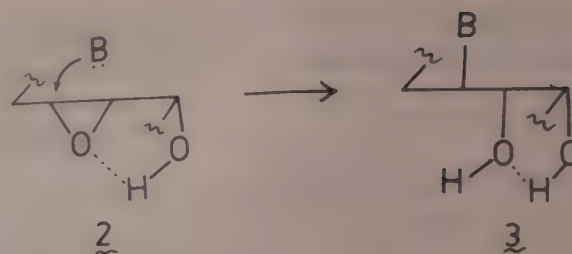
#### (B) Hydrogen bonding in *cis*-epoxyalcohols

Another example of the use of the CSD arose from a synthetic study where stereospecific ring opening of an epoxy pyranoside (2) was the key-step towards the polyhydroxy derivative (3). Unfortunately base attack at the alternative site was also possible and would lead to the undesired product (4). However, it was felt that the presence of the *cis*-hydroxyl group would

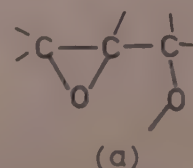


favour intramolecular hydrogen bonding and that such bonding would cause a preference for ring-opening to 3 rather than to 4.<sup>28</sup>

The structural question then became: How effective is intramolecular hydrogen bonding between an



epoxide and an *cis*-hydroxyl group in such pyranoses/pyranosides? This is an example of a problem where the fragment in question is so uncommon that a conventional library search would be very difficult. Indeed, the 1983 version of the CSD showed not even a single structure for an epoxy pyranose/pyranoside with a *cis*-hydroxyl group. The CONNSER query was thus relaxed to include acyclic derivatives with the fragment (a).



This operation resulted in eight independent structure determinations with the above fragment occurring a total of nine times. Table 3 gives the literature references for seven compounds while Fig. 2 gives the structural formulae. Table 3 was obtained after excluding one compound (Refcode MEZERE) whose coordinates are not given in the CSD. It may further be noted from Fig. 2 that the compound GUVACO, while formally fulfilling the requirements of the CONNSER query, is chemically quite different from the other retrieved compounds being an epoxy acid rather than an epoxyalcohol. Hence this compound may also be rejected. Likewise, the hydroxy group in the compound EPXBIM (a tautomeric amide structure) is much more acidic than the hydroxy group in an epoxy alcohol and thus this compound is also discarded.

Let us turn our attention to the compounds BIYKOJ, DANGAL10, DANGAL11, DHCMYD10, and OVALDB. The structures DANGAL10 and DANGAL11 are polymorphs of 1,2-5,6-dianhydrogalactitol. While the former has one molecule in the asymmetric unit, the latter (P1, Z=2, each half molecule on a distinct inversion centre) has two independent molecules in the crystal. These molecules have different conformations which have been termed A and B by the authors. We shall use the same notation here. Newman projections of these conformations about the C-C bond linking the epoxide ring and the hydroxyl group are represented by conformations (A-C).

Table 3—*cis*-Epoxyalcohols on the Cambridge Structural Database Literature References

Selection Criteria: Literature references for *cis*-epoxyalcohols with published or deposited co-ordinates. The REFCODE (BIYKOJ for the first entry) is a six-letter code (plus a two-digit acronym where necessary) that uniquely determines the crystal structure entry in the CSD.

4,7-Oxido-7-methyl-7-hydroxymethyl-2,2,6,6-tetramethylpiperidin-1-oxyl,

BIYKOJ, Cygler M, *Can J Chem*, **60** (1982) 2392.

1,2,5,6-Dianhydrogalactitol (alpha form)

DANGAL10, Czugler M, Simon K, Institoris L, Vidra I & Csoregh I, *Carbohydr Res*, **108** (1982) 173.

1,2,5,6-Dianhydrogalactitol (beta form)

DANGAL11, Czugler M, Simon K, Institoris L, Vidra I & Csoregh I, *Carbohydr Res*, **108** (1982) 173.

Dihydrochlamydocin monohydrate

DHCMYD10, Flippen J L & Karle I L, *Biopolymers*, **15** (1976) 1081.

2,3-Epoxy-1-hydroxy-2,3-dimethylbutanimine

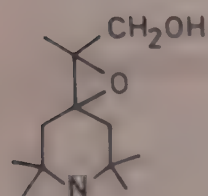
EPXBIM, Powell J E, Osuch C, Burkholder H R, Kulprathipanja S, Miller J H, Stadherr L G & Baughman R G, *J Org Chem* **43** (1978) 3166.

(3*RS*, 4*SR*)-3,4-Epoxypiperidine-3-carboxylic acid monohydrate Guvacine oxide monohydrate

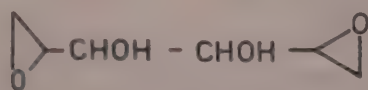
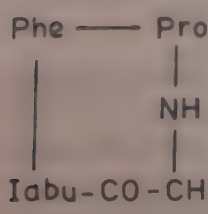
GUVACO, Krogsgaard-Larsen P, Jacobsen P, Brehm L, Larsen J & Schwumburg K, *Eur J Med Chem-Chim Theor*, **15** (1980) 529.

Ovalicine dibromide (absolute configuration)

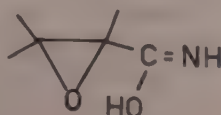
OVALDB, Bollinger P, Sigg H P & Weber H P, *Helv chim Acta*, **56** (1973) 819.



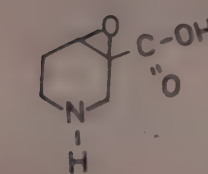
BIYKOJ

DANGAL 10 (Alpha Form)  
DANGAL 11 (Beta Form)

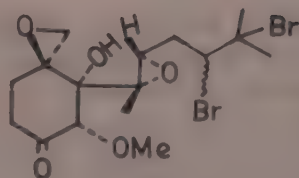
DHCMYD 10



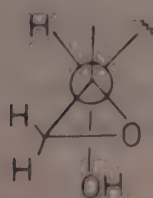
EPXBIM



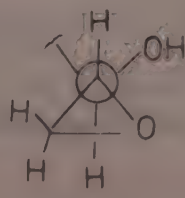
GUVACO



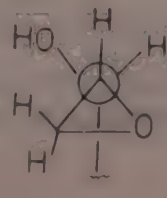
OVALDB



A



B



C

In the DANGAL10 structure, only the (A) conformation is present. The third possible conformation (C) is found in one of the epoxide rings in the compound OVALDB. Geometrical calculations

with GEOM 78 show that the respective torsion angles about the central C—C bond fall within narrow ranges for these conformations. While intramolecular hydrogen bonding may be possible in conformations (A) and (B), it is clearly difficult in (C). A convenient way of monitoring these effects is to compare the shortest intra- and inter-molecular non-bonded contacts involving the epoxide hydroxyl oxygen atoms and Table 4 gives some relevant details. This approach is a useful one since the presence of intramolecular H-bonds in the crystal (where intermolecular effects may compete) is a good indication that such bonds will persist in solution (where intermolecular H-bonds are not so important).

Examination of Table 4 shows that in all the B-conformations, intermolecular H-bonding is predominant while intramolecular H-bonding is not so important. Note that the ranges of O...O distances are very small even though entirely different crystal structures are being compared; 2.77, 2.78 and 2.81 Å for intermolecular contacts and 3.07, 3.08 and 3.13 Å for intramolecular ones. In the C-conformation in

Table 4—Intra- and Inter-molecular O...O Distances in a Series of *cis*-Epoxyalcohols

Compd Refcode	Conformation Type	Shortest Intra-molecular distance (Å)	Shortest Inter-molecular distance (Å)
BIYKOJ	B	3.13	2.77
DANGAL10	A	2.87	2.82
DANGAL11	A	2.84	2.87
DANGAL11	B	3.07	2.81
DHCMYD10	B	3.08	2.78
OVALDB	A	2.56	> 3.10
OVALDB	C	3.69	> 3.10

OVALDB both intra- and inter-molecular H-bondings are probably absent. On the other hand, the greatest likelihood of intramolecular H-bonding is in the A-conformation. While intra- and inter-molecular effects are evenly matched in DANGALIO and DANGALII, intramolecular H-bonding is probably quite important in the A-conformation ring of OVALDB.

Construction of models then showed that the incorporation of the A-conformation in a pyranose skeleton is possible but that the O...O distance would perhaps be slightly longer than in the acyclic cases. The tentative conclusion of this analysis is that intramolecular hydrogen-bonding between an epoxide and a hydroxyl group in a pyranoside such as 2 is of marginal importance with H-bonding to other molecules and solvent perhaps being alternative competitive processes in solution.

### Conclusions

One of the advantages of Database Research in the context of activities in India is that it is being studied in only a few laboratories abroad. Therefore, there is a good prospect of obtaining interesting results by researchers who embark upon work in this area now. Organic chemists with access to good computing systems with graphics capabilities might find this a fruitful area of research and be able to work competitively.

### Acknowledgements

The review portions of this paper were presented at a DST-PAC workshop on an 'Organic Chemistry Update' held at the Indian Institute of Science, Bangalore in July 1984. Thanks are due to Dr. F.H. Allen, Cambridge Crystallographic Data Centre for kindly reading this paper prior to submission, supplying statistical information on the CSD and for permission to reproduce Figure 1 from his lecture notes for the 10th International Summer School on Crystallography: Static and Dynamic Implications of Precise Structural Information, Erice, Sicily, May-June 1985.

### References and Notes

Many of the references given below cover important

aspects of Database research. An exhaustive list of references to papers dealing with the CSD and related studies is provided in the lecture notes by F.H. Allen referred to above. These notes are to appear as part of a book in the near future.

- 1 Stout G H & Jensen L H, *X-ray structure determination, a practical guide* (Collier-Macmillan, London), 1968.
- 2 Dunitz J D, *X-ray analysis and the structure of organic molecules* (Cornell University Press, Ithaca), 1979.
- 3 Woolfson M M, *An introduction to X-Ray crystallography* (Cambridge-Vikas, New Delhi) 1980.
- 4 Kitaigorodskii A I, *Molecular crystals and molecules* (Academic Press, New York) 1973.
- 5 Allen F H, Bellard S, Brice M D, Cartwright B A, Doubleday A, Higgs H Hummelink T, Hummelink-Peters B G, Kennard O, Motherwell W D S, Rodgers J R, & Watson D G, *Acta Crystallogr*, **B35** (1979) 2331.
- 6 *Molecular structures and dimensions*, Vols 1-15, edited by O Kennard, D G Watson, F H Allen, S A Bellard & B A Carwright (D. Reidel, Dordrecht), 1970-1984.
- 7 Allen F H & Kennard O, *Perspectives in computing* (IBM Corp.), **3** (1983) 28.
- 8 Burgi H B & Dunitz J D, *Acc Chem Res*, **16** (1983) 153.
- 9 Allen F H, Kennard O & Taylor R, *Acc Chem Res*, **16** (1983) 146.
- 10 Domenicano A & Murray-Rust P, *Tetrahedron Lett*, (1979) 2283 and other references cited in reference 8.
- 11 Allen F H, *Acta Crystallogr, Sect B*, **36** (1980) 81.
- 12 Britton D & Dunitz J D, *J Am chem Soc*, **103** (1981) 2971.
- 13 Burgi H B, *Angew Chem intern Edn*, **14** (1975) 460.
- 14 Muller K, *Angew Chem intern Edn*, **19** (1980) 1.
- 15 Allen F H & Kirby A J, *J Am chem Soc*, **106** (1984) 6197 and the two succeeding papers by Jones P G & Kirby A J.
- 16 Murray-Rust P & Glusker J P, *J Am chem Soc*, **106** (1984) 1018 and the references cited therein.
- 17 Taylor R & Kennard O, *Acc Chem Res*, **17** (1984) 320.
- 18 Taylor R, Kennard O & Versichel W, *J Am chem Soc*, **106** (1984) 244.
- 19 Taylor R & Kennard O, *J Am chem Soc*, **104** (1982) 5063.
- 20 Jeffrey G A & Sundaralingam M, *Adv Carbohydr Chem & Biochem*, **38** (1981) 176.
- 21 Thomas N W & Desiraju G R, *Chem Phys Lett*, **110** (1984) 99.
- 22 Sarma J A R P & Desiraju G R, *Chem Phys Lett*, **117** (1985) 160.
- 23 Rosenfield R E, Parthasarathy R & Dunitz J D, *J Am chem Soc*, **99** (1977) 4860.
- 24 Desiraju G R & Sarma J A R P, *Chem Commun*, (1983) 45.
- 25 Sarma J A R P & Desiraju G R, *J chem Soc Perkin Trans-II*, (1985) (in press).
- 26 Cohen M D, Schmidt G M J & Sonntag F I, *J chem Soc*, (1964) 2000.
- 27 Holden J R & Dickinson C, *J phys Chem*, **81** (1977) 1505.
- 28 Nagarajan M, Personal Communication (1984).

## Asymmetric Synthesis of *R*-(−)-2-Acetyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene—A Key Synthon for Synthesis of 11-Deoxyanthracyclines†

A V RAMA RAO\*, BHANU CHANDA, H B BORATE & MANISHA GUPTA

National Chemical Laboratory, Pune 411 008

Received 8 July 1985; accepted 9 August 1985

A practical synthesis of *R*-(−)-2-acetyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene is achieved from (±)-2-(α-hydroxyethyl)-5-methoxy-1,4-dihydronaphthalene (**5**) making use of Sharpless' asymmetric epoxidation.

11-Deoxydaunomycin (**1**) and 11-deoxyadriamycin (**2**), the two second generation anthracyclines are important natural antitumour antibiotics exhibiting strong antineoplastic activity similar to that of adriamycin (**3**) but with less cardiotoxicity<sup>1</sup>. Although a few syntheses of racemic aglycone of 11-deoxydaunomycin (11-deoxydaunomycinone, **4**) have been reported including our two different approaches<sup>2</sup>, to this date only one asymmetric synthesis of 11-deoxydaunomycinone has been reported by Kishi and his group<sup>3</sup>. In this paper, we would like to report our findings on the asymmetric synthesis of the AB synthon which can be elaborated to various natural and synthetic 11-deoxyanthracyclines.

Our approach towards an asymmetric synthesis of **4** is centred around the methodology of Wong *et al.* for assembling the tetracyclic system involving AB + CD coupling<sup>4</sup>. We have earlier successfully completed the synthesis of (±)-4-demethoxy-11-deoxydaunomycinone by this approach utilising (±)-2-(α-hydroxyethyl)-5-methoxy-1,4-dihydronaphthalene (**5**) prepared from 1,5-dihydroxynaphthalene<sup>5</sup>. **5** has now been converted into *R*-(−)-2-acetyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**6**) adopting Sharpless' asymmetric synthesis (kinetic method)<sup>6</sup>. This method is simple and akin to that reported earlier by us for the synthesis of *R*-(−)-2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene which was further elaborated to 4-demethoxydaunomycinone<sup>7</sup>.

As per the predictions by Sharpless *et al.*<sup>6</sup> the stereochemical outcome of the kinetic resolution in the epoxidation of racemic secondary allylic alcohol is clear. Upon use of a given tartrate isomer, the delivery of the epoxide oxygen is from the same enantioface of the olefin regardless of the substitution pattern. It is

generally observed that when using L(+)-tartrates, the fast reacting enantiomer corresponds to *S*-enantiomer and there is preferential erythro selectivity in the product formed. On the other hand, when D(−)-tartrate is used, *R*-enantiomer is the faster reacting one. Thus, it is obvious that in our system, viz. **5**, we have to employ D(−)-tartrate to obtain the required *R*-(−)-**6**.

Kinetic resolution of the racemic allylic alcohol (**5**) was carried out at −50° by treating (±)-**5**<sup>5</sup> in CH<sub>2</sub>Cl<sub>2</sub> with titanium tetrakisopropoxide, D(−)-diisopropyl tartrate [D(−)-DIPT]<sup>8</sup> followed by *t*-butyl hydroperoxide (TBHP) in a molar ratio of 1:1:0.6 (vide Experimental). The optically active epoxy alcohol (**7**) was separated from the unreacted antipode of the allylic alcohol, *S*(−)-**8** by silica gel chromatography and purified by crystallisation from hexane. The epoxide was obtained in 98% enantiomeric excess (ee), determined by converting **7** into its Mosher ester (with α-methoxy-α-trifluoromethyl phenylacetic acid) followed by <sup>1</sup>H NMR analysis in the presence of Eu(fod)<sub>3</sub>. Reduction of **7** with LiAlH<sub>4</sub> in tetrahydrofuran followed by chromatographic purification furnished the diol, *R*-(−)-2-(*R*-1-hydroxyethyl)-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**9**) in 81% yield.

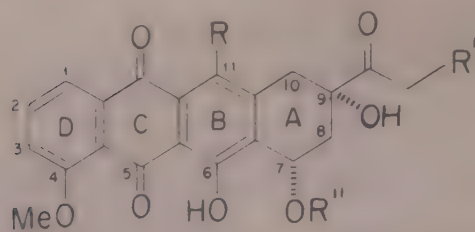
Selective oxidation of **9** with Fetizon's reagent<sup>9</sup> (Ag<sub>2</sub>CO<sub>3</sub>-celite) gave *R*-(−)-**6** in 81% yield. It was crystallised twice from CCl<sub>4</sub>-hexane to obtain a constant rotation value of −28.09°.

The above series of reactions was similarly carried out with L(+)-DIPT to obtain the other isomer *S*(+)-**11** (see Experimental).

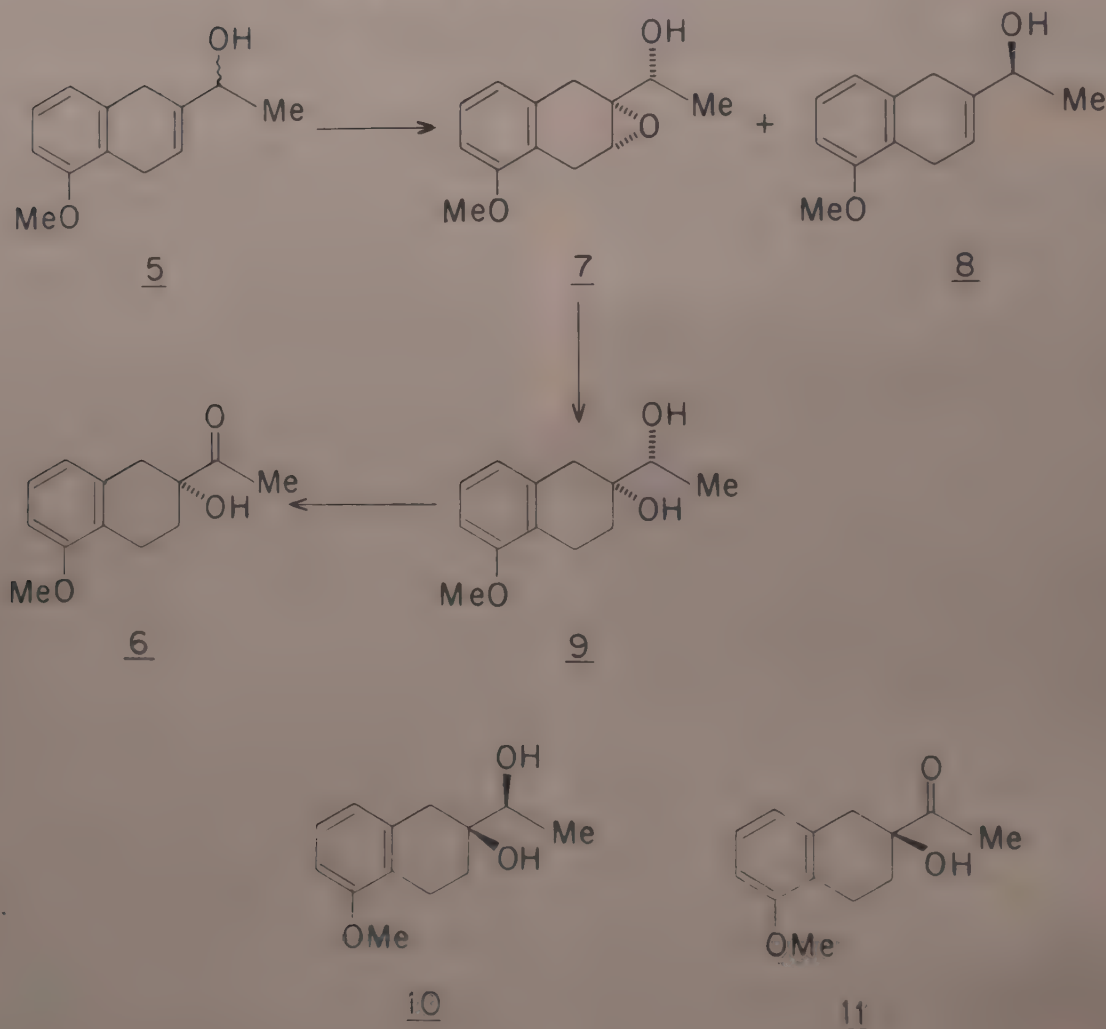
### Experimental Procedure

Melting points are uncorrected. IR spectra ( $\nu_{\max}$  in cm<sup>−1</sup>) were recorded in nujol or thin films on a Perkin-Elmer model 683 spectrophotometer with sodium chloride optics, PMR spectra on Varian A-60 or

†NCL Communication No. 3790



- 1  $R = R' = H, R'' = \text{daunosaminy}$
- 2  $R = H, R' = OH, R'' = \text{daunosaminy}$
- 3  $R = R' = OH, R'' = \text{daunosaminy}$
- 4  $R = R' = R'' = H$



Varian FT-80A or Bruker WH-90 spectrometer in  $\text{CDCl}_3$  using TMS as an internal standard; chemical shifts are expressed in  $\delta$ -scale (ppm). Mass spectra were run on an AEI MS 30 double beam mass spectrometer or CEC 21-110B mass spectrometer with direct inlet system. All solvents and reagents were purified by standard techniques.

#### Sharpless' epoxidation of (+)-5

A two-necked flask flushed with nitrogen and cooled to  $-50^\circ\text{C}$  was charged with  $\text{CH}_2\text{Cl}_2$  (40 ml), titanium tetraisopropoxide (426 mg, 1.5 mmol) and D (-)-DIPT (351 mg, 1.5 mmol). The mixture was stirred

at  $-50^\circ\text{C}$  for a few minutes. To this were added the allylic alcohol (5) (306 mg, 1.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 ml) followed by TBHP (0.2 ml of 4.4 M solution, 0.9 mmol) and the stirring at  $-50^\circ\text{C}$  was continued for 7 hr. The progress of the reaction was monitored by titrating the concentration of TBHP. Usual work-up<sup>6</sup> gave a mixture of two products (7) and (8) which were separated by silica gel column chromatography. The optically active epoxy alcohol (7) was crystallised from hexane in colourless needles, m.p.  $102-3^\circ$ , yield 45 mg (46%);  $[\alpha]_D^{20} + 81.61^\circ$  (c, 0.035,  $\text{CHCl}_3$ ); IR (nujol) 3450 and  $1600\text{ cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ): 1.23 (d, 3H,  $J = 7\text{ Hz}$ ), 3.80 (s, 3H), 6.45-7.35 (m, 3H).

The unreacted antipode of the allylic alcohol (**8**) was recovered in 47% yield,  $[\alpha]_D^{20} -128.3^\circ$  (*c*, 0.042,  $\text{CHCl}_3$ ).

*R*-(−)-2-(*R*-1-Hydroxyethyl)-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**9**)

To a stirred solution of  $\text{LiAlH}_4$  (57 mg, 1.5 mmol) in dry ether (5 ml) was added **7** (220 mg, 1 mmol) and the mixture stirred at ambient temperature for 30 min. The reaction mixture was worked-up in the usual manner and the product purified by silica gel chromatography. The unstable diol (**9**) (180 mg, 81%) was obtained as a colourless crystalline solid, m.p.  $62-64^\circ$ ,  $[\alpha]_D^{20} -12.24^\circ$  (*c*, 0.36,  $\text{CHCl}_3$ ); IR(neat): 3440 and 1600; PMR( $\text{CDCl}_3$ ): 1.28(*d*, 3H,  $J=7$  Hz), 1.74(*bs*, 1H), 1.96(*bs*, 1H), 2.78-3.28(*m*, 6H), 3.86(*q*, 1H,  $J=7$  Hz), 4.10(*s*, 3H), 7.03-7.83(*m*, 3H).

*R*-(−)-2-Acetyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**6**)

The diol (**9**, 399 mg, 1.8 mmol) and freshly prepared Fetizon's reagent<sup>9</sup> (5 mmol) were heated under reflux in dry benzene (30 ml) with azeotropic removal of water during 1.5 hr. The reaction mixture was filtered, washed with benzene, concentrated and purified by silica gel chromatography. The crude solid obtained was crystallised twice from  $\text{CCl}_4$ -hexane to give **6** as colourless plates, m.p.  $87-88^\circ$ , yield 320 mg (81%),  $[\alpha]_D^{20} -28.09^\circ$  (*c*, 0.84,  $\text{CHCl}_3$ ); IR(nujol): 3480, 1715 and 1600; PMR( $\text{CDCl}_3$ ): 2.25(*s*, 3H), 3.80(*s*, 3H), 6.50-7.25(*m*, 3H); MS: *m/z* 220 ( $\text{M}^+$ ).

Sharpless' epoxidation of (±)-**5** using *L*(+)-DIPT

The allylic alcohol (**5**, 306 mg, 1.5 mmol) was epoxidised as described above but using *L*(+)-DIPT. After carrying out the reaction under identical conditions, the epoxy alcohol obtained was crystallised from hexane to yield colourless needles, m.p.  $99-100^\circ$ , yield 130 mg (41.5%);  $[\alpha]_D^{20} -81.98^\circ$  (*c*, 0.04,  $\text{CHCl}_3$ ). The IR and PMR spectra were identical in all respects with the epoxy alcohol (**7**) obtained using *D*(−)-DIPT.

*S*(+)-2-(*S*-1-Hydroxyethyl)-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**10**)

Reduction of the above alcohol (220 mg, 1 mmol) with  $\text{LiAlH}_4$ , as described for the *R*-isomer, afforded after usual work-up and purification, the diol (**10**) as a colourless solid, m.p.  $61-62^\circ$ , yield 170 mg (76.5%);  $[\alpha]_D^{20} +11.11^\circ$  (*c*, 0.36,  $\text{CHCl}_3$ ).

*S*(+)-2-Acetyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**11**)

The above diol (**10**, 399 mg, 1.8 mmol) was oxidised with Fetizon's reagent as described above for the *R*-isomer. After the usual work-up, the crude solid was crystallised twice from  $\text{CCl}_4$ -hexane to yield **11** as colourless plates, m.p.  $86-87^\circ$ , yield 280 mg (71.8%);  $[\alpha]_D^{20} +26.5^\circ$  (*c*, 0.04,  $\text{CHCl}_3$ ).

### Acknowledgement

This work was supported in part by a grant from the Science & Technology Cell, Education & Youth Services Department, Government of Maharashtra.

### References

- 1 Arcamone F, *Doxorubicin: Antitumour antibiotic—A series of monographs*, Vol. 17 (Academic Press, New York), 1981.
- 2 Rama Rao A V, Deshpande V H & Laxma Reddy N, *Tetrahedron Lett*, **23** (1982) 775; Rama Rao A V, Mehendale A R & Bal Reddy K, *Tetrahedron Lett*, **23** (1982) 2415; Rama Rao A V, Mehendale A R & Bal Reddy K, *Tetrahedron Lett*, **24** (1983) 1093. See also Rama Rao A V, *Proc Indian Acad Sci*, **93** (1984) 1059 and references cited therein.
- 3 Sekizaki H, Jung M, McNamara J M & Kishi Y, *J Am chem Soc*, **104** (1982) 7372.
- 4 Wong C M, Popien D, Schwenk R & Te Raa J, *Can J Chem*, **49** (1971) 2712.
- 5 Rama Rao A V, Chanda B M & Borate H B, *Syn Commun*, **14** (1984) 257.
- 6 Martin V S, Woodward S S, Katsuki T, Yamada Y, Ikeda M & Sharpless K B, *J Am chem Soc*, **103** (1981) 6237; Katsuki T & Sharpless K B, *J Am chem Soc*, **102** (1980) 5974; Sharpless K B, *Pure & Appl chem*, **55** (1983) 589.
- 7 Rama Rao A V, Yadav J S, Bal Reddy K & Mehendale A R, *Chem Commun*, (1984) 453; *Tetrahedron*, **40** (1984) 4643.
- 8 Prepared as per the procedure reported in *J chem Soc*, (1928) 1831.
- 9 Fetizon M & Golfier M, *C hehd Acad Sci Paris*, **267** (1968) 900.

## Synthesis of 6-Methyl-11-demethylellopticine

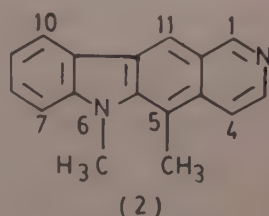
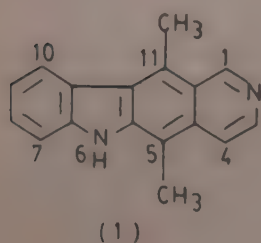
N S NARASIMHAN\* & D D DHAVALE†

Department of Chemistry, University of Poona, Pune 411 007

Received 21 June 1985; accepted 31 July 1985

The synthesis of 6-methyl-11-demethylellopticine (**2**) from the readily accessible N-methyltetrahydrocarbazole (**4**) is described. Condensation of **4** with 2, 2-dimethoxyethylamine furnishes the azomethine (**5**), which undergoes acid-catalysed cyclisation with orthophosphoric acid (91%) to furnish **2** as a yellow solid.

Indole alkaloids of the ellopticine (**1**) series, isolated from the plants of the genus *Aspidosperma* (fam: Apocynaceae), show marked anticancer and anti-tumor activities<sup>1</sup>. The findings<sup>2</sup> that the N-methylellopticine analogues have significant anticancer activity is particularly interesting. We describe in this paper the synthesis of 6-methyl-11-demethylellopticine (**2**), which is not reported so far.



The starting compound, 3-formyl-1, 9-dimethyl-carbazole (**3**)<sup>3</sup> obtained by Vilsmeier-Haack reaction of N-methyltetrahydrocarbazole (**4**), on condensation with 2, 2-dimethoxyethylamine in benzene furnished the azomethine (**5**).

The acid-catalysed cyclisation of the azomethine (**5**) with 91% orthophosphoric acid at 130° yielded a yellow solid, m.p. 140-50° (45%), which analysed for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>, in accord with its cyclic nature. The PMR data (see Experimental), indicated that it was a mixture of two isomers, presumably, **2** and **6**. Our attempts to separate the mixture by column chromatography were unsuccessful. However, repetitive recrystallization from ethyl acetate-pet. ether (1:1) gave a pale yellow crystalline solid, m.p. 156° (10%). The PMR spectrum of the compound displayed two singlets of three protons each at  $\delta$  3.78 and 2.75 assignable to -NCH<sub>3</sub> and Ar-CH<sub>3</sub> groups respectively and other signals at  $\delta$  9.12 (s, 1H, 1-H), 8.35 (d, 1H, 3-H,  $J=6$ Hz), 8.09 (s,

1H, 11-H), 7.96 (dd, 1H, 10-H,  $J=7$  and 2Hz), 7.63 (d, 1H, 4-H,  $J=6$ Hz), 7.58-7.0 (m, 3H, Ar-H). This indicated that the isolated product was a single compound and could have either structure **2** or **6**. However, the appearance of four low field signals, two singlets at  $\delta$  9.12 and 8.09, one doublet at 8.35 and one doublet of doublet at 7.96, supported structure (**2**) for this compound. Structure (**2**) is expected to show four low field signals: two singlets for C<sub>1</sub>-H and C<sub>11</sub>-H, one doublet for C<sub>3</sub>-H and one doublet of doublet for C<sub>10</sub>-H; C<sub>10</sub>-H and C<sub>11</sub>-H are mutually deshielded protons due to close proximity. Likewise structure (**6**) should also display four low field signals: one singlet for C<sub>4</sub>-H, two doublets for C<sub>2</sub>-H and C<sub>1</sub>-H and one doublet of doublet for C<sub>11</sub>-H; C<sub>1</sub>-H and C<sub>11</sub>-H are mutually deshielded protons due to close proximity. The UV spectrum of the compound, which was analogous to ellopticine (**1**)<sup>4</sup> also indicated a linear structure as in **2**.

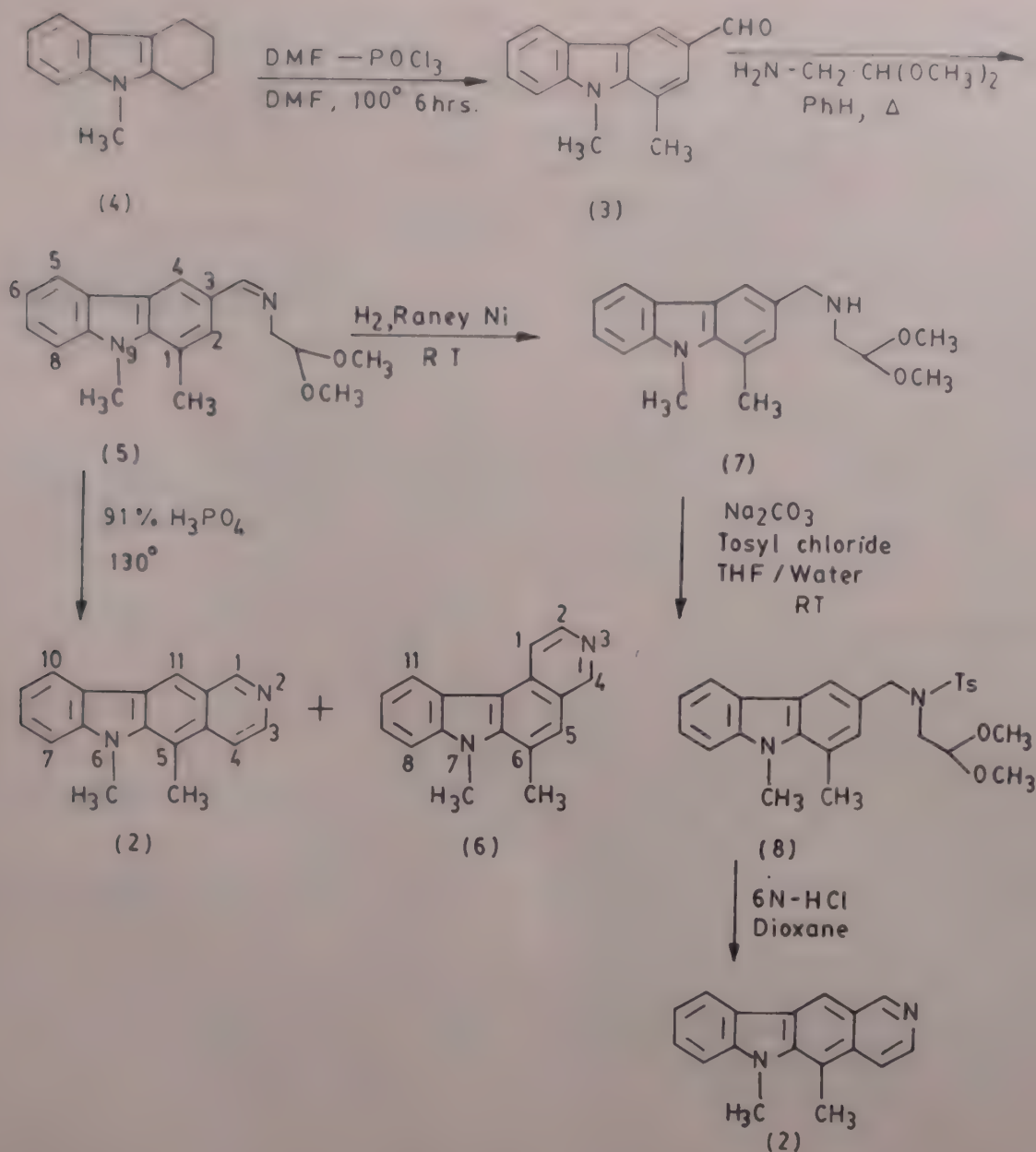
Our efforts to obtain the angularly cyclized 6, 7-dimethylpyrido [3,4-c] carbazole (**6**) in its pure form from the mixture obtained above were unsuccessful.

Attempts to synthesise **2**, exclusively from the azomethine (**5**), using other cyclodehydrating reagents such as TFA, H<sub>2</sub>SO<sub>4</sub>, POCl<sub>3</sub>, ethanol-dry HCl etc. met with failure. Finally **2** was synthesised in good yields according to a known<sup>5</sup> procedure. Thus, **5** was reduced to the amine (**7**) (70%), which was tosylated to **8** (83%). Compound **8** underwent cyclization with 6N HCl in dioxane to afford exclusively **2** in 38% yield.

### Experimental Procedure

All melting points are uncorrected. UV spectra ( $\lambda_{max}$  in nm, log  $\epsilon$  values in parentheses) were recorded in MeOH on a Beckman UV-5260 spectrophotometer. IR spectra in nujol ( $\nu_{max}$  in cm<sup>-1</sup>) on a Perkin-Elmer instrument model 337 and PMR spectra in CDCl<sub>3</sub> on a Perkin-Elmer R-32, 90 MHz instrument. chemical shifts are expressed in  $\delta$  (ppm) downfield from TMS internal standard.

\*Taken from the Ph.D. dissertation of D.D. Dhavale submitted to the University of Poona in February 1984.



### 3-(2,2-Dimethoxyethyliminomethyl)-1,9-dimethylcarbazole (5)

A mixture of 3-formyl-1,9-dimethylcarbazole<sup>4</sup> (3, 3.2 g) and 2,2-dimethoxyethylamine (2 ml) was refluxed in dry benzene for 2 hr. Removal of water by azeotropic distillation (twice) and removal of solvent under reduced pressure gave a yellow solid, which recrystallised from benzene-pet. ether (1:1) to give 5 as a pale yellow solid (3.9 g, 86%); m.p. 91-93°; (Found: C, 73.4; H, 7.1.  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$  requires C, 73.5; H, 7.1%); IR: 1640, 1600, 1230, 915; PMR: 8.32 (bs, 1H,  $-\text{N}=\text{CH}-$ ), 8.16 (d, 1H, 4-H,  $J=2\text{Hz}$ ), 8.02 (dd, 1H, 5-H,  $J=8$  and  $2\text{Hz}$ ), 7.57 (d, 1H, 2-H,  $J=2\text{Hz}$ ), 7.48-7.05 (m, 3H, Ar-H), 4.71 [t, 1H,  $-\text{CH}_2-\text{CH}(\text{OCH}_3)_2$ ,  $J=5.5\text{Hz}$ ], 3.93 (s, 3H,  $-\text{NCH}_3$ ), 3.80 (bd, 2H,  $=\text{NCH}_2-$ ,  $J=5.5\text{Hz}$ ), 3.43 (s, 6H,  $2 \times \text{OCH}_3$ ), 2.75 (s, 3H, Ar- $\text{CH}_3$ ).

### 6-Methyl-11-demethylellipticine (2)

To orthophosphoric acid (91%, 25 ml), maintained at 130°, was added 5 (1 g) with constant stirring. The

reaction mixture was further heated for 20 min, cooled to room temperature, poured into cold water, filtered, the filtrate basified with ammonia and precipitate extracted with chloroform ( $3 \times 75$  ml). The combined chloroform extract was washed with water and extracted with 1% hydrochloric acid ( $4 \times 100$  ml). The acid extract was warmed at 50-60° for 30 min, filtered, the filtrate basified with 40N NaOH, cooled and the yellow precipitate obtained extracted with chloroform ( $3 \times 75$  ml). The chloroform extract was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and solvent removed under reduced pressure. Chromatography over neutral alumina using chloroform-pet. ether (7:3) as eluent furnished yellow solid (0.36 g, 45%), m.p. 140-50°. Repetitive crystallisation (5 times) with ethyl acetate-pet. ether (1:1) gave pale yellow solid (0.08 g, 10%), m.p. 156° (Found: C, 82.8; H, 5.8.  $\text{C}_{17}\text{H}_{14}\text{N}_2$  requires C, 82.9; H, 5.7%); UV: 226 (4.43), 240 (4.15), 275 (4.65), 285 (4.79), 295 (4.96), 330 (3.84), 345 (3.44), 380 (3.51), 395 (3.43); IR: 1615, 1290, 1240, 1135, 855, 800.

3-(2,2-Dimethoxyethylaminomethyl)-1,9-dimethylcarbazole (7)

A solution of **5** (1 g) in methanol (20 ml) was hydrogenated for 4 hr at 60 psi and room temperature over Raney nickel. The solution was filtered, the filtrate concentrated under reduced pressure and the residue recrystallised from benzene-pet. ether (1:1) to afford **7** as a colourless solid (0.7 g, 70%), m.p. 43-45° (Found: C, 73.2; H, 7.8.  $C_{19}H_{24}N_2O_2$  requires C, 73.0; H, 7.7%); IR: 1600, 1460, 1376, 1350, 1330, 1230, 1190, 1140, 1060; PMR: 8.03 (*dd*, 1H, 5-H,  $J=7.5$  and 2Hz), 7.85 (*d*, 1H, 4-H,  $J=2$ Hz), 7.55-7.03 (*m*, 4H, Ar-H), 4.53 [*t*, 1H,  $-CH_2-CH(OCH_3)_2$ ,  $J=6$ Hz], 4.04 (*s*, 3H,  $-NCH_3$ ), 3.93 (*s*, 2H, Ar- $CH_2-N<$ ), 3.38 (*s*, 6H,  $2 \times OCH_3$ ), 2.82 (*m*, 5H, Ar- $CH_3$  and  $>N-CH_2-CH<$ ), 1.73 (*s*, 1H,  $-NH$ , exchangeable with  $D_2O$ ).

3-N[(*p*-Toluenesulphonyl)-(2,2-dimethoxyethylamino)-methyl]-1,9-dimethylcarbazole (8)

A mixture of **7** (1.2 g), sodium carbonate (0.5 g) in tetrahydrofuran (25 ml) and water (15 ml) was stirred at room temperature for 15 min. *p*-Toluenesulphonyl chloride (0.5 g) was then added and the reaction mixture stirred for further 2 hr. Dilution with water, extraction with chloroform and usual work-up gave **8**, a yellow solid, which crystallised from ethanol as colourless crystals (1.5 g, 83%), m.p. 106-8° (Found: C, 67.0; H, 6.5.  $C_{26}H_{30}N_2O_4S$  requires C, 66.9; H, 6.5%); IR: 1600, 1160, 1130, 1078, 920; PMR: 7.97-7.65 (*m*, 3H, 5-H, 2' and 6'-H), 7.55 (*bs*, 1H, 4-H), 7.5-7.05 (*m*,

5H, Ar-H), 6.93 (*bs*, 1H, 2-H), 4.61 (*s*, 2H, Ar- $CH_2-$ ), 4.43 [*t*, 1H,  $(H_3CO)_2-CH-$ ,  $J=6$ Hz], 4.03 (*s*, 3H,  $-NCH_3$ ), 3.29 [*bs*, 8H,  $2 \times OCH_3$ ,  $(H_3CO)_2-CH-CH_2-$ ], 2.75 (*s*, 3H, Ar- $CH_3$ ), 2.42 (*s*, 3H, Ts- $CH_3$ ).

6-Methyl-11-demethylellipticine (2)

To a precooled (10-15°) mixture of dioxane (20 ml) and 6 *N* hydrochloric acid (5 ml), **8** (1 g) was added. The solution was stirred at 10-15° for 20 hr, poured into water (50 ml), filtered, the filtrate basified with 2 *N* sodium hydroxide and precipitate extracted with chloroform ( $3 \times 100$  ml). Usual work-up and removal of solvent at reduced pressure gave a yellow solid. Chromatography over alumina using chloroform as eluent and crystallisation from ethyl acetate-pet. ether (1:1) gave **2** (0.2 g, 38%) as pale yellow crystals, m.p. 156°, identical (m.m.p. and spectral data) with **2** obtained above.

References

- 1 Woodward R B, Iacobucci G A & Hochstein F A, *J Am chem Soc*, **81** (1959) 4434.
- 2 Le Pecq J B, Gosse C, Dat-Xuong N & Paoletti C, *C R Acad Sci Ser D*, **227** (1973) 2289; *Proc natl Acad Sci USA*, **71** (1974) 5078.
- 3 Narasimhan N S & Dhavale D D, *Indian J Chem*, **23B** (1984) 199.
- 4 Granwell P A & Saxton J E, *J chem Soc*, (1962) 3482.
- 5 Birch A J, Jackson A H & Shannon P V R, *J chem Soc Perkin Trans-I*, (1974) 2185.

## A New Total Synthesis of C-20 Functionalised Ring-C Aromatic 18-Norsteroid

SWARAJ B MAITI, A P KUNDU, AMARESHWAR CHATTERJEE & S R RAYCHAUDHURI\*

Department of Chemistry, Jadavpur University, Calcutta 700 032

Received 21 June 1985; accepted 22 July 1985

Total synthesis of 10-methyl-3-oxogonane-4,8,11,13-tetraene-17 $\beta$ -carboxylic acid (**7b**) and the corresponding methyl ester (**7a**) are reported. Lithium-liquid ammonia reduction of **7b** affords 10 $\beta$ -methyl-3-oxo-5 $\alpha$ (*H*)-gonane-8,11,13-triene-17 $\beta$ -carboxylic acid (**8**) and 3 $\beta$ -hydroxy-10 $\beta$ -methyl-5 $\alpha$ (*H*)-gonane-8,11,13-triene-17 $\beta$ -carboxylic acid (**9**) which is found to be identical with the metal-ammonia reduction product of the ketoacid (**8**) using alcohol as the proton source.

Ring-C aromatic steroids have the molecular topology similar to that of natural steroids. Viridin<sup>1</sup> is the first isolated naturally occurring ring-C aromatic steroid possessing remarkably high fungistatic activity. Partial synthesis of ring-C aromatic steroids through aromatisation of ring-C of suitably substituted steroids with concomitant migration of C-13 methyl group to C-12 or C-17 has been explored by various groups<sup>2,3</sup>. Transformation of diterpenoids to various ring-C aromatic steroids has also been reported in literature<sup>4-6</sup>. Wagner-Meerwin shift of 13 $\beta$ -methyl to 17 $\beta$ -position has been extensively studied by Hewett *et al.*<sup>7</sup> to prepare several 11-hydroxy ring-C aromatic steroids. These procedures, however, are not always suitable for introducing desired functionalities at the important positions of the molecule.

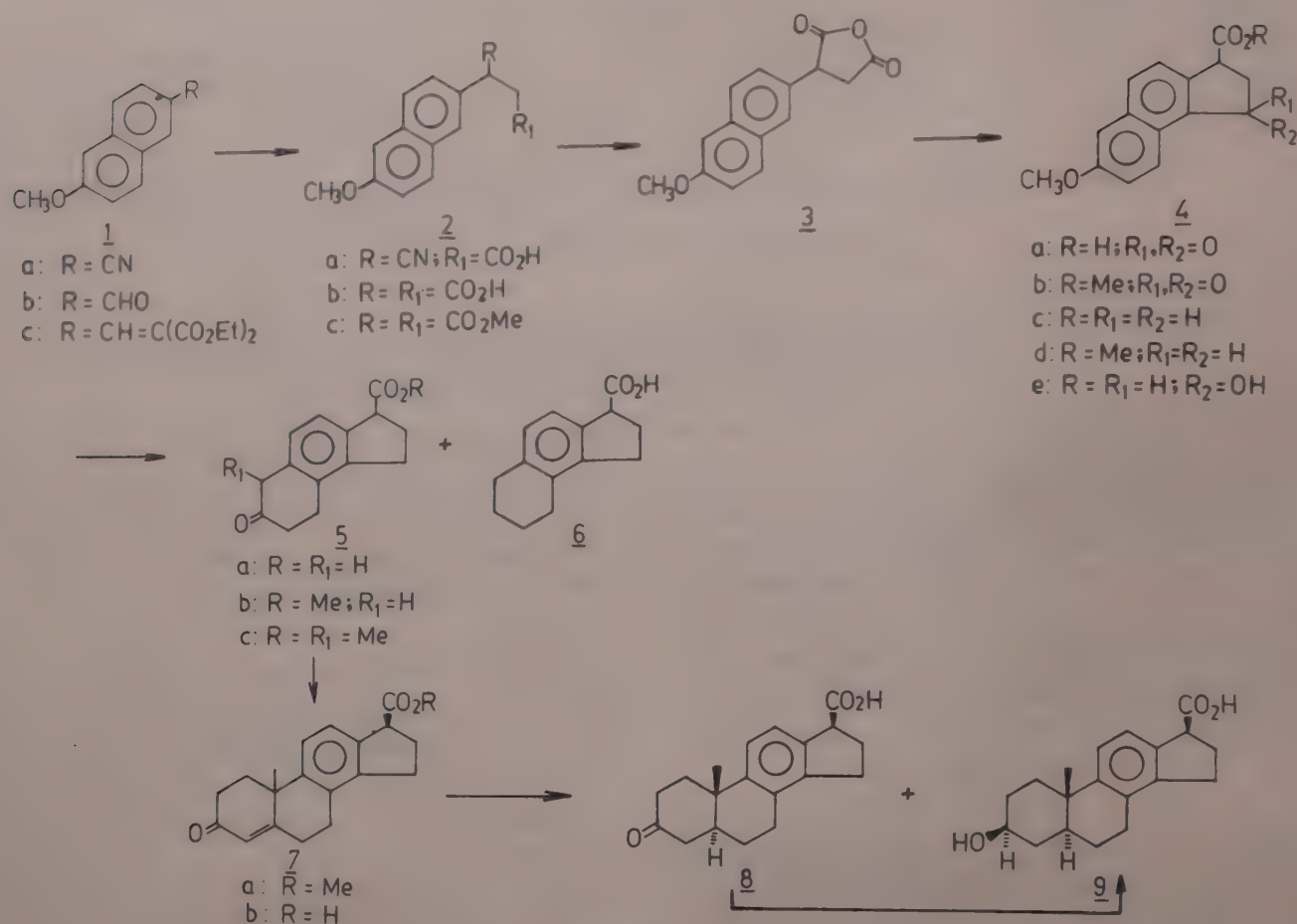
Synthesis of ring-C aromatic bis-norsteroids was reported by Birch *et al.*<sup>8</sup> and Windholz and coworkers<sup>9</sup>. The first total synthesis of ring-C aromatic steroid with C-10 methyl group and steroidal oxygenation pattern at C-3, C-11 and C-17 was disclosed from our laboratory<sup>10</sup>. A similar synthesis of ring-C aromatic steroid was also achieved by one of our associates<sup>11</sup> from different laboratory; and the synthesis reported by Razdan and his associates<sup>12</sup> is essentially that of ours<sup>10</sup> with minor modifications in some steps. Recently, a new class of ring-C aromatic steroids, having *cis*-fused A-B ring, have been isolated<sup>13</sup> from geological sources, and the total synthesis<sup>14</sup> of a tetracyclic steroidal intermediate of this class has recently been reported from our laboratory.

Herein we wish to record a new total synthesis of C-20 functionalised ring-C aromatic steroids through BC  $\rightarrow$  BCD  $\rightarrow$  ABCD approach as shown in Scheme 1.

2-Cyano-6-methoxynaphthalene (**1a**), obtained from 2-bromo-6-methoxynaphthalene<sup>15</sup> following the literature procedure<sup>16</sup>, was converted into the aldehyde (**1b**) in very high yield following the

procedure of Staskun *et al.*<sup>17</sup>. It may be pointed out that the above conversion under refluxing condition<sup>18</sup> was not successful in our hand. Use of stannous chloride and dry hydrogen chloride for the above transformation<sup>19</sup> was also not very encouraging from the preparative point of view. Knoevenagel condensation<sup>20</sup> of **1b** with diethyl malonate provided in excellent yield the expected naphthylidenemalonate (**1c**). Addition<sup>21</sup> of potassium cyanide to **1c** followed by acidification afforded  $\beta$ -cyano- $\beta$ -(6-methoxy-2-naphthyl) propionic acid (**2a**) in very good yield, which on acid hydrolysis<sup>22</sup> furnished the succinic acid derivative (**2b**) in near quantitative yield. Acid (**2b**) was further purified through its methyl ester (**2c**). Attempted PPA cyclisation of **2b** to the ketoacid (**4a**) at 170-80° was not rewarding **2b** was converted into the anhydride (**3**), and this on intramolecular Friedel-Crafts cyclisation<sup>22</sup> with some modification (see Experimental) provided the crude benzindanone derivative (**4a**). Esterification of **4a** by diazomethane followed by chromatography afforded the crystalline ketoester (**4b**) in overall good yield. The ketoester (**4b**) exhibited characteristic IR bands at 1722 and 1700 cm<sup>-1</sup> and UV maximum at 247 nm ( $\epsilon$  35,720). The appearance of an aromatic proton at  $\delta$  9.05 as doublet and keto-methylene group at  $\delta$  3.05 as double doublets in its PMR spectrum established its structure as **4b**. Alkaline hydrolysis of **4b** under nitrogen provided in high yield the desired crystalline ketoacid (**4a**).

Huang-Minlon or Raney-nickel reduction at elevated temperature<sup>23</sup> of **4a** to **4c** were unsuccessful. Clemmensen reduction of **4a**, however, afforded the **4c** in only 42% yield. It may be mentioned that the **4b** remained unchanged when its solution in cyclohexene was refluxed<sup>24</sup> with a mixture of 10% Pd-C and anhydrous FeCl<sub>3</sub>. Catalytic hydrogenolysis of **4b** over PtO<sub>2</sub> in acetic acid and perchloric acid followed by alkaline hydrolysis of the resulting reduced product finally provided **4c** in moderate yield. The reduced



SCHEME 1

ester (4d) was finally obtained† in high yield when 4b was hydrogenolysed over 10% Pd-C in acetic acid containing a catalytic amount of perchloric acid. Appearance of benzylic two-proton multiplet at  $\delta$  3.10-3.43 in the PMR spectrum of 4d and disappearance of the carbonyl band at  $1700\text{ cm}^{-1}$  in its IR spectrum provided convincing support to structure (4d). Sodium-liquid ammonia reduction of 4c using ethanol as the proton source and subsequent hydrolysis with dil. hydrochloric acid‡ provided the desired  $\beta$ -tetralone derivative (5a) in acceptable yield, together with a small amount of demethoxylated product (6). Attempted conversion of the hydroxyacid (4e), obtained through sodium borohydride reduction of 4a, directly to 5a through Birch reduction using methanol as the proton source was disappointing as this provided 5a in poor yield along with 6. Such reductive removal of the methoxyl group during Birch reduction of the related system is well-documented in the literature<sup>10</sup>. The structure of the 5a was supported by the appearance of a band at  $1700\text{ cm}^{-1}$  in its IR spectrum in presence of triethylamine, and a characteristic two-proton singlet at  $\delta$  3.57 for the

benzylic methylene in its PMR spectrum. The ketoacid (5a) furnished the corresponding methyl ester (5b) by usual esterification with diazomethane.

Methylation of 5b through its pyrrolidine enamine<sup>25</sup> by refluxing the enamine with  $\text{CH}_3\text{I}$  in methanol<sup>26</sup> provided the desired 5c in only 22% yield. Use of acetonitrile as a solvent<sup>27</sup>, instead of methanol, dramatically increased the yield of 5c to 56%. In the PMR spectrum the methyl group and the benzylic ketomethine protons in 5c appeared as a doublet at  $\delta$  1.40 and a quartet at 3.37 respectively.

Condensation of 5c with methyl vinyl ketone in the presence of catalytic amount of sodium methoxide followed by aldolisation of the resulting crude product with aqueous potassium hydroxide furnished an acidic material which on usual esterification ( $\text{CH}_2\text{N}_2$ ) afforded the non-crystalline tetracyclic ketoester (7a) in reasonably good yield. Alkaline hydrolysis of 7a, however, furnished the crystalline tetracyclic ketoacid (7b). It may be mentioned here that the above ring annelation reaction using methiodide of 1-diethyl-amino-3-butanone and sodium methoxide as reported for the related system<sup>10</sup> afforded 7b in lower yield. Attempted equilibration of 7a with methanolic sodium methoxide was unsuccessful, the starting 7a being recovered, showing thereby that C-17 ester function in 7a has most probably the stable quasi-equatorial  $\beta$ -configuration.

†Small amount of the acid (4c) was also isolated from the above experiment as a result of partial hydrolysis of 4d under the reaction condition.

‡Use of aqueous oxalic acid for hydrolysis slightly reduced the yield of 5a.

Lithium-liquid ammonia reduction of **7b** using ammonium chloride as the proton source resulted in a mixture of products which on chromatographic purification afforded in respectable yield the saturated ketoacid (**8**, 45%), and the hydroxyacid (**9**, 13%). The *trans*-stereochemistry of the A/B ring fusion in **8** and **9** follows from the well known stereochemical course of Birch reduction of the related system<sup>10,28</sup>. The hydroxyacid (**9**) is formed as a result of further reduction of the desired ketoacid (**8**) under the reaction condition. The structure of the hydroxyacid as **9** was supported by an independent experiment as described below. The above ketoacid (**8**) on lithium-liquid ammonia reduction using *t*-butanol as the proton source afforded in good yield, the same hydroxyacid (**9**) mentioned above. The  $\beta$ -configuration of the hydroxy group at C-3 as shown in **9** is supported by the fact<sup>29</sup> that metal-ammonia reduction of unhindered carbonyl groups in the presence of alcohol affords the more stable alcohol in predominant amount.

The carboxyl group at C-17 on **7-9** should serve as a handle for the introduction of side chain as present in cortisone and other related steroid hormones at C-17.

### Experimental Procedure

The compounds described are racemic. Melting points are uncorrected. UV spectra were recorded in ethanol on a Unicam SP 500 spectrophotometer ( $\lambda_{\max}$  in nm), IR spectra in chloroform on a Perkin-Elmer 337 instrument ( $\nu_{\max}$  in  $\text{cm}^{-1}$ ) and PMR spectra, unless otherwise stated in  $\text{CDCl}_3$  on a Varian T-60 spectrometer using TMS as internal standard (chemical shift in  $\delta$ , ppm). Pet. ether refers to the fraction b.p. 60-80° and the extracts were dried over anhydrous sodium sulphate.

#### Diethyl (6-methoxy-2-naphthylidene)malonate (**1c**)

A mixture of 6-methoxy-2-naphthaldehyde<sup>18</sup> (**1b**, 20 g), diethyl malonate (25 ml), piperidine (3.2 ml) and benzoic acid (0.5 g) in dry benzene (280 ml) was refluxed for 16 hr using Dean-Stark water separator. The reaction mixture was cooled to room temperature, diluted with water (150 ml), the benzene layer separated and the aqueous layer thoroughly extracted with ether (3  $\times$  75 ml). The combined organic extract was washed successively with cold dil HCl (3%, 3  $\times$  50 ml), aq.  $\text{NaHCO}_3$  (2  $\times$  50 ml), cold water and dried. Removal of solvent furnished crude **1c** as a reddish brown oil which was distilled under reduced pressure (32 g), b.p. 210-20° (bath)/0.2 mm, m.p. 89-91°, and recrystallised from ether-pet. ether to furnish pure **1c** (28.5 g, ~81%), m.p. 92-93°; IR: 1725, 1620, 1600; UV: 257 ( $\epsilon$  22,060), 278 ( $\epsilon$  25,080), 332 ( $\epsilon$  25,250); PMR: 1.27 (3H, *t*,  $J$  = 8 Hz), 1.33 (3H, *t*,  $J$  = 8 Hz), 3.90 (3H, *s*), 4.30 (2H, *q*,  $J$  = 8 Hz), 4.37 (2H, *q*,  $J$  = 8 Hz), 7.07 (1H, *bs*),

7.10-7.20 (1H, complex *m*), 7.42 (1H, *dd*,  $J$  = 2 and 9 Hz) and 7.50-7.93 (4H, *m*) (Found: C, 69.5; H, 6.0.  $\text{C}_{19}\text{H}_{20}\text{O}_5$  requires C, 69.5; H, 6.1%).

#### $\beta$ -Cyano- $\beta$ -(6-methoxy-2-naphthyl) propionic acid (**2a**)

To a solution of **1c** (11.2 g) in ethanol (85 ml) was added a solution of potassium cyanide (60% purity, 4.7 g) in water (9 ml) and refluxed with stirring at 80-85° for 18 hr when a solid separated out. The reaction mixture was cooled to 5-10°, the precipitated solid filtered and washed with little cold water and ethanol. The solid obtained was stirred with dil HCl (6N, 50 ml) at room temperature for 2 hr and extracted with ether (4  $\times$  125 ml). Usual processing of the combined organic extract afforded **2a** (8.28 g, 95%); m.p. 126-28° (ether-pet. ether); IR: 2245, 1725, 1630, 1602 (Found: C, 70.4; H, 5.0; N, 5.4.  $\text{C}_{15}\text{H}_{13}\text{NO}_3$  requires C, 70.6; H, 5.1; N, 5.5%).

#### $\alpha$ -(6-Methoxy-2-naphthyl)succinic acid (**2b**)

The crude cyanoacid (**2a**, 8.28 g) was hydrolysed by heating under reflux for 18 hr with a mixture of conc HCl (13.5 ml) and water (68 ml). The reaction mixture was cooled to 5°, the pink coloured solid filtered, washed thoroughly with cold water and dried to furnish **2b** (7.8 g, 88%); m.p. 210-11° (MeOH); IR (nujol): 1710 (Found: C, 65.4; H, 5.1.  $\text{C}_{15}\text{H}_{14}\text{O}_5$  requires C, 65.7; H, 5.2%).

#### Dimethyl $\alpha$ -(6-methoxy-2-naphthyl)succinate (**2c**)

A mixture of **2b** (10.2 g), dry methanol (100 ml) and conc  $\text{H}_2\text{SO}_4$  (10 ml) was refluxed for 20 hr, cooled in ice-bath, the separated solid filtered, washed with ice-cold methanol and dried to furnish crude **2c** (10.22 g). Removal of methanol from the filtrate and usual processing of the residue afforded some additional amount of **2c** (1.25 g). Recrystallisation from ether-pet. ether furnished pure **2c** (10.5 g, 93%); m.p. 120-21°; IR: 1730, 1635, 1601; PMR: 2.50-2.90 (1H, *m*), 3.03-3.50 (1H, *m*), 3.70 (6H, *s*), 3.90 (3H, *s*), 4.10-4.33 (1H, *m*), 7.07-7.30 (3H, *m*), 7.40-7.63 (2H, *m*) and 7.70 (1H, *d*,  $J$  = 8 Hz) (Found: C, 67.3; H, 6.0.  $\text{C}_{17}\text{H}_{18}\text{O}_5$  requires C, 67.5; H, 6.0%).

#### 3-Carbomethoxy-7-methoxybenz [*e*]indan-1-one (**4b**)

A mixture of **2b** (3 g) and acetic anhydride (13.5 ml) was heated on a steam-bath for 3 hr under anhydrous condition. Removal of excess acetic anhydride from the reaction mixture initially under reduced pressure and finally at 95°/2 mm for 1 hr provided the crude  $\alpha$ -(6-methoxy-2-naphthyl)succinic anhydride (**3**) as a light yellow solid (2.8 g); IR: 1863, 1780. This was used in the next step as such.

To an ice-cold and stirred solution of anhydrous  $\text{AlCl}_3$  (5.4 g) in dry nitrobenzene (45 ml) was added

during 3 hr at 0°C, a solution of **3** (2.8 g) in dry nitrobenzene (45 ml). Stirring was continued at 0°C for a further period of 2 hr, and then left at room temperature for 16 hr. The reaction mixture was then quenched with cold water (90 ml) and conc HCl (30 ml). Nitrobenzene was removed by steam-distillation and the residual brown oil extracted with ether-methylene chloride (4 × 100 ml). Usual processing of the combined organic extract furnished crude 3-carboxy-7-methoxybenz[e]indan-1-one (**4a**) as a brown solid (2.8 g).

The crude **4a** (6 g) in ether (50 ml) was treated with an ethereal solution of diazomethane (prepared from 7.5 g of nitrosomethylurea). Usual work-up provided a solid (5.5 g), which was recrystallised from ether-pet ether to afford pure **4b** (3 g); m.p. 109-10°. The residue from the mother liquor, on chromatography over silica gel (7.5 g, 35% ether-pet. ether) afforded an additional amount of pure **4b** (0.9 g), m.p. 109-10°. Total yield of **4b** was 3.9 g [62% based on the diacid (**2b**)]; IR: 1722, 1700, 1630, 1601; UV: 247 ( $\epsilon$  35,720); PMR: 2.65-3.45 (2H, *m*), 3.77 (3H, *s*), 3.90 (3H, *s*), 4.22-4.42 (1H, *m*), 7.17-7.42 (2H, *m*), 7.63 (1H, *d*, *J* = 9 Hz), 7.95 (1H, *d*, *J* = 9 Hz) and 9.05 (1H, *d*, *J* = 9 Hz) (Found: C, 71.0; H, 5.0. C<sub>16</sub>H<sub>14</sub>O<sub>4</sub> requires C, 71.1; H, 5.1%); 2,4-DNP, m.p. 258-59° (d) (benzene) (Found: C, 58.6; H, 4.1; N, 12.4. C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>7</sub> requires C, 58.7; H, 4.0; N, 12.4%).

Hydrolysis of **4b** with KOH followed by usual work-up afforded the corresponding acid (**4a**) which recrystallised from CH<sub>2</sub>Cl<sub>2</sub>-MeOH; m.p. 165-66°; IR: 1705, 1628, 1604; with Et<sub>3</sub>N: 1700; UV: 246 ( $\epsilon$  42,400) (Found: C, 70.3; H, 4.9. C<sub>15</sub>H<sub>12</sub>O<sub>4</sub> requires C, 70.3; H, 4.7%).

### 3-Carboxy-7-methoxybenz[e]indane (**4c**): (i) *By catalytic hydrogenolysis of 4b over Pd-C (10%)*

A solution of **4b** (2 g) in gl AcOH (30 ml) was hydrogenated over 10% Pd-C (0.4 g) in the presence of perchloric acid (5 drops). The catalyst was filtered, the filtrate diluted with cold water and the product extracted with ether (4 × 100 ml). The combined organic extract was successively washed with water, aq. NaHCO<sub>3</sub> and water. Removal of the solvent furnished a light yellow solid (1.85 g), a portion of which was recrystallised from ether-pet. ether to furnish pure ester (**4d**); m.p. 98-99°; IR: 1722, 1625, 1600; PMR: 2.40-2.67 (2H, *m*), 3.10-3.43 (2H, *m*), 3.71 (3H, *s*), 3.87 (3H, *s*), 4.17 (1H, *t*, *J* = 7 Hz), 7.00-7.23 (2H, *m*) and 7.37-7.53 (3H, *m*) (Found: C, 74.9; H, 6.4. C<sub>16</sub>H<sub>16</sub>O<sub>3</sub> requires C, 75.0; H, 6.3%).

Acidification of the above bicarbonate extract followed by usual work-up furnished an acid (0.12 g), m.p. 184-85°, which was found to be identical with the triphic acid (**4c**) described above.

The above crude tricyclic ester (**4d**, 4.7 g) was hydrolysed by heating under reflux for 3 hr with methanolic KOH (5%, 55 ml) under nitrogen atmosphere. Usual work-up afforded a crude acid (4.05 g) which on crystallisation provided the desired **4c** (2.5 g), m.p. 187-88° (MeOH).

Residue from the mother liquor of the above crystallisation was chromatographed over silica gel (50 g, 20% ether-pet. ether) to afford additional amount of **4c** (0.25 g; overall yield 67%); IR: 1705, 1635, 1600 (Found: C, 74.3; H, 5.7. C<sub>15</sub>H<sub>14</sub>O<sub>3</sub> requires C, 74.4; H, 5.8%).

### (ii) *Through catalytic hydrogenolysis of 4b over PtO<sub>2</sub>*

A solution of **4b** (0.2 g) in AcOH (4.5 ml) containing perchloric acid (4 drops) was hydrogenated over PtO<sub>2</sub> (0.04 g). Processing as above resulted in a red oily product (0.19 g) which was hydrolysed by refluxing with methanolic KOH (2.6%, 5 ml) for 3 hr under nitrogen atmosphere. After usual work-up, the crude product was obtained as solid (0.16 g). Chromatography over silica gel (6.4 g, 20% ether(pet ether)) afforded **4c** (0.07 g, 37%), m.p. 187-88° (ether-pet ether).

### (iii) *By Clemmensen reduction of ketoacid (4a)*

A mixture of **4a** (0.2 g), toluene (10 ml), conc HCl (8 ml), water (2 ml) and amalgamated zinc (2 g) was refluxed for 9 hr (after 4 hr and 6 hr intervals 5 ml of conc HCl and 1 g of amalgamated zinc was added to the reaction mixture). The organic layer was separated and the aqueous layer extracted with ether. The combined organic acid was leached with aq bicarbonate, the bicarbonate extract acidified with conc HCl in the cold and the liberated acid extracted with ether (4 × 20 ml). Removal of the solvent after usual processing afforded a yellowish sticky material (0.15 g), which on chromatography over silica gel (4.5 g, 20% ether-pet ether) furnished **4c** (0.08 g, 42%), m.p. 187-88° (MeOH); IR: 1705, 1635, 1600.

### 3-Carboxy-1-hydroxy-7-methoxybenz[e]indane (**4e**)

To an ice-cold solution of **4a** (0.6 g) in aq NaOH (1.7%, 15 ml), NaBH<sub>4</sub> (0.24 g) was added portionwise with stirring during 40 min. The stirring was continued at this temperature for further 2 hr and left for 16 hr at room temperature. Usual work-up furnished the desired **4e** (0.56 g, ~93%), m.p. 152-54° (methylene chloride-methanol); IR: 3500-3450, 1705, 1625, 1600; with Et<sub>3</sub>N, no carbonyl band (Found: C, 70.0; H, 5.2. C<sub>15</sub>H<sub>14</sub>O<sub>4</sub> requires C, 69.8; H, 5.5%).

### 3-Carboxy-7-oxo-6,7,8,9-tetrahydrobenz[e]indane (**5a**) and 3-carboxy-6,7,8,9-tetrahydrobenz[e]indane (**6**): (i) *Sodium-liquid ammonia reduction of 4c*

To undistilled liquid ammonia (350 ml), one small piece of sodium metal was added with vigorous stirring

when a blue colour developed. To this was quickly added a solution of the **4c** (1 g) in dry THF (75 ml). Small pieces of sodium metal (0.57 g) were then added to the stirred solution during 1.5 min. The reaction mixture was treated with anhydrous EtOH (6 ml) when the blue colour was discharged. Ammonia was evaporated within 20 min, the residue diluted with water (100 ml) and acidified with cold dil HCl (3 N, 40 ml). EtOH (15 ml) was added to the acidified mixture and the resulting solution refluxed on a steam-bath for 15 min. THF was removed under reduced pressure and the residue diluted with water (200 ml). The product that separated was extracted with ether (4 × 60 ml). Usual processing of the organic extract afforded a yellowish orange solid (0.95 g), which was crystallised from ether-pet ether to furnish pure **5a** (0.41 g), m.p. 149-50°. Residue from the mother liquor, on chromatography over silica gel (15 g, 25% ether-pet ether) furnished an additional amount of **5a** (0.08 g; overall ~52%); IR: 1700; with Et<sub>3</sub>N, 1700; PMR: 2.18-2.67 (4H, *m*), 2.80-3.20 (4H, *m*), 3.57 (2H, *s*), 4.07 (1H, *t*, *J* = 7 Hz), 6.93 (1H, *d*, *J* = 8 Hz), 7.26 (1H, *d*, *J* = 8 Hz) and 9.57 (1H, *bs*) (Found: C, 72.9; H, 6.4. C<sub>14</sub>H<sub>14</sub>O<sub>3</sub> requires C, 73.0; H, 6.1%).

Elution of the chromatogram initially with 15% ether-pet ether afforded the undesired **6** (0.01 g, 1%), m.p. 120-22° (pet ether); IR: 1710; MS: *m/z* 216 (M<sup>+</sup>), 171 (M<sup>+</sup>-CO<sub>2</sub>H); PMR: 1.69-1.94 (3H, *m*), 2.25-3.0 (9H, *m*), 4.0 (1H, *t*, *J* = 7.5 Hz), 6.89 (1H, *d*, *J* = 7.5 Hz) and 7.13 (1H, *d*, *J* = 7.5 Hz).

(ii) *By sodium-liquid ammonia reduction of 4e*

To a stirred solution of sodium (0.55 g) in liquid ammonia (250 ml) was added a solution of **4e** (0.4 g) in THF (25 ml) during 5 min. After 30 min of stirring, dry MeOH (4 ml) was added dropwise during 2 min. Work-up of the reaction mixture as above afforded the crude product (0.3 g) which on crystallisation from pet ether furnished the desired **5a** (0.12 g, 34%), m.p. 149-50°.

Residue from the mother liquor (0.18 g) on chromatography over silica gel (5 g, 15% ether-pet ether) provided the undesired **6** (0.04 g, 12%), m.p. 120-22° (pet ether).

*3-Carbomethoxy-7-oxo-6,7,8,9-tetrahydro-benz[e]indane (5b)*

Esterification of **5a** (1 g) with diazomethane [prepared from nitrosomethylurea (1.35 g)] in the usual way furnished **5b** as a brown oil (0.95 g, 85%), b.p. 160-70°/0.1 mm; IR: 1730; PMR: 2.20-2.67 (4H, *m*), 2.80-3.20 (4H, *m*), 3.53 (2H, *s*), 3.70 (3H, *s*), 4.03 (1H, *t*, *J* = 7 Hz), 6.87 (1H, *d*, *J* = 8 Hz) and 7.17 (1H, *d*, *J* = 8 Hz); 2,4-DNP, m.p. 219-20° (chloroform-methanol) (Found: C, 59.4; H, 4.7; N, 13.3. C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub> requires C, 59.4; H, 4.8; N, 13.2%).

*3-Carbomethoxy-6-methyl-7-oxo-6,7,8,9-tetrahydrobenz[e]indane (5c)*

To a solution of **5b** (0.925 g) in dry benzene (25 ml), were added dry pyrrolidine (1.2 ml) and PTS (0.005 g) and the resulting mixture refluxed with Dean and Stark water separator for 3.5 hr. Complete removal of the solvent and excess pyrrolidine under reduced pressure afforded a light brown solid (1.15 g); IR: 1725, 1610, 1595. This was used in the next step as such.

The above crude enamine (1.15 g) was dissolved in dry acetonitrile (26 ml) and treated with methyl iodide (6 ml). The reaction mixture was refluxed under nitrogen for 16 hr at 60-65°C. Removal of excess methyl iodide and solvent under reduced pressure afforded a gummy solid which was hydrolysed by heating with a mixture of acetic acid (2 ml), chloroform (1 ml) and water (8 ml) under nitrogen for 1.5 hr at 90-95°. The reaction mixture was cooled to room temperature and diluted with chloroform (75 ml). Organic layer was separated and the aqueous layer extracted with ether (2 × 40 ml). Usual processing of the combined organic extract afforded (**5c**) as brown oil which was purified by evaporative distillation to furnish pure **5c** (0.62 g, 63%), b.p. 160-65° (bath)/0.1 mm; IR: 1722, 1625; PMR (CCl<sub>4</sub>): 1.37 (3H, *d*, *J* = 7 Hz), 2.20-2.63 (4H, *m*), 2.63-3.10 (4H, *m*), 3.33 (1H, *q*, *J* = 7 Hz), 3.67 (3H, *s*), 3.92 (1H, *t*, *J* = 7 Hz), 6.87 (1H, *d*, *J* = 8 Hz) and 7.13 (1H, *d*, *J* = 8 Hz); 2,4-DNP, m.p. 199-200° (chloroform-methanol) (Found: C, 60.2; H, 5.4; N, 12.7. C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O<sub>6</sub> requires C, 60.3; H, 5.1; N, 12.8%).

*Methyl 10-methyl-3-oxogonane-4,8,11,13-tetraene-17β-carboxylate (7a)*

To a stirred and ice-cold solution of **5c** (0.215 g) in anhydrous methanol (3 ml) was added under nitrogen, a methanolic solution of NaOMe (0.286 ml containing 2.8 mg of sodium). After 15 min, freshly distilled methyl vinyl ketone (0.088 ml) was added during 3 hr to the cold reaction mixture with stirring. Stirring was continued at 0° for further 3 hr, left overnight in the refrigerator, diluted with brine (25 ml) and extracted with ether (4 × 15 ml). Usual work-up of the organic extract afforded a viscous oil (0.24 g). After removal of low boiling material at 155-60°/0.1 mm, the residue was refluxed for 2 hr under nitrogen with a solution of KOH (0.15 g) in water (1 ml) and methanol (2.5 ml). Usual work-up of the reaction mixture afforded a non-crystalline acid (0.185 g), IR: 1710, 1665, 1625; with Et<sub>3</sub>N, 1665 and 1625. Esterification of this acid with diazomethane in the usual way furnished a red viscous oil (0.2 g) which was evaporatively distilled to provide the pure **7a** (0.15 g, 58%), b.p. 180-90° (bath)/0.1 mm, as a light yellow viscous oil; IR: 1725, 1665, 1605; UV: 232 (ε 17,390); MS: *m/z* 310 (M<sup>+</sup>), 295 (M<sup>+</sup> - CH<sub>3</sub>),

258, 236; PMR ( $\text{CCl}_4$ ): 1.53 (3H, s), 1.80-2.90 (12H, m), 3.67 (3H, s), 3.87 (1H, t,  $J=7$  Hz), 5.70 (1H, s), 6.97 (1H, d,  $J=8$  Hz) and 7.13 (1H, d,  $J=8$  Hz); 2,4-DNP, m.p. 123-24° (chloroform-methanol) (Found: C, 63.4; H, 5.4; N, 11.4.  $\text{C}_{26}\text{H}_{26}\text{O}_6\text{N}_4$  requires C, 63.7; H, 5.3; N, 11.4%).

10-Methyl-3-oxogonane-4,8,11,13-tetraene-17 $\beta$ -carboxylic acid (7b)

7a (0.26 g) was hydrolysed by heating under reflux with a solution of KOH (0.11 g) in water (0.5 ml) and methanol (1.5 ml) for 2 hr under nitrogen atmosphere. Usual work-up followed by regeneration of the crude acid from aq.  $\text{NaHCO}_3$  extract afforded 7b as a solid (0.211 g, 85%); m.p. 188-91° (methanol-ether); IR: 1710, 1665, 1625; UV: 232 ( $\epsilon$  18,360); MS:  $m/z$  296 ( $\text{M}^+$ ), 281 ( $\text{M}^+ - \text{CH}_3$ ); PMR: 1.56 (3H, s), 1.94-3.0 (12H, m), 4.06 (1H, t,  $J=7$  Hz), 5.88 (1H, s), 7.13 (1H, d,  $J=8$  Hz) and 7.31 (1H, d,  $J=8$  Hz) found: C, 76.8; H, 6.5.  $\text{C}_{19}\text{H}_{20}\text{O}_3$  requires C, 77.0; H, 6.8%.

Lithium-liquid ammonia reduction of 7b: Formation of 10 $\beta$ -methyl-3-oxo-5 $\alpha$ (H)-gonane-8,11,13-triene-17 $\beta$ -carboxylic acid (8) and 3 $\beta$ -hydroxy-10 $\beta$ -methyl-5 $\alpha$ (H)-gonane-8,11,13-triene-17 $\beta$ -carboxylic acid (9)

To undistilled liquid ammonia (175 ml) was added small pieces of lithium metal (45 mg) and stirred for 1 min when a blue solution resulted. A solution of 7b (0.2 g) in dry THF (14 ml) was added to this blue solution within 1 min. with stirring. Stirring was continued for further 2.5 min, the reaction mixture quenched with solid  $\text{NH}_4\text{Cl}$  (0.78 g) and ammonia evaporated within 25 min. The residual brown solid was dissolved in cold water (30 ml) and acidified with dil HCl (1N, 20 ml) under cold condition. The product was extracted with ether-methylene chloride (4  $\times$  25 ml), and the combined organic extract washed with cold brine and dried. Removal of the solvent furnished a yellowish foamy mass which was chromatographed over silica gel (7 g). Elution with ether-pet ether (25%) afforded 8 as a crystalline solid (0.097 g, 48%), m.p. 199-201° (ether); IR: 1710, 1600; MS:  $m/z$  298 ( $\text{M}^+$ ), 283 ( $\text{M}^+ - \text{CH}_3$ ), 253 ( $\text{M}^+ - \text{CO}_2\text{H}$ ); PMR: 1.3 (3H, s), 1.52-2.20 (5H, complex m), 4.06 (1H, t,  $J=7$  Hz), 7.18 (1H, d,  $J=8$  Hz) and 7.28 (1H, d,  $J=8$  Hz) (Found: C, 76.4; H, 7.3.  $\text{C}_{19}\text{H}_{22}\text{O}_3$  requires C, 76.5; H, 7.4%).

Further elution with ether-pet ether (35%) furnished 9 (0.027 g, 13%), m.p. 241-44° (ether-pet ether). MS:  $m/z$  300 ( $\text{M}^+$ ), 285 ( $\text{M}^+ - \text{CH}_3$ ), 261 ( $\text{M}^+ - \text{CH}_3 - \text{H}_2\text{O}$ ), 185 ( $\text{M}^+ - \text{CO}_2\text{H}$ ) (Found: C, 76.2; H, 7.9.  $\text{C}_{19}\text{H}_{24}\text{O}_3$  requires C, 76.0; H, 8.1%).

Compound 9 was also obtained by the treatment of 8 with lithium-liquid ammonia as described above.

Acknowledgement

We thank Dr D Mukherjee, IACS, Calcutta for PMR spectra, Prof Dr B C Das, ICSN, CNRS, France for mass spectra of some of the compounds and the UGC, New Delhi, for financial support.

References

- Grove J F, *J chem Soc (C)*, (1969) 549 & references therein.
- (a) Hammer C F, Savage D S, Thomson J B & Stevenson R, *Tetrahedron*, **20** (1964) 929.
- (b) Margulis T N, Hammer C F & Stevenson R, *J chem Soc*, (1964) 4396.
- (c) Edmunds R, Midgley J M, Tagg L G, Wilkins B J & Whalley W B, *J chem Soc Perkin Trans-1*, (1978) 76.
- (d) Levy D & Stevenson R, *Tetrahedron Lett*, (1966) 3063.
- (e) Meney J, Kim Y H, Stevenson R & Margulis T N, *Chem Commun*, (1970) 1706.
- (f) Meney J, Kim Y H, Stevenson R & Margulis T N, *Tetrahedron*, **29** (1973) 21.
- (a) Turner A B, *J chem Soc Perkin Trans-I*, (1979) 1333 & references therein.
- (b) Cheung H T A, McQueen R G, Vadasz A & Watson T R, *J chem Soc Perkin Trans-I*, (1979) 1048.
- (a) Davins B R & Watkins W B, *Tetrahedron*, **24** (1968) 2165.
- (b) Davis B R & Watkins W B, *Aust J Chem*, **21** (1968) 1611.
- (c) Wheeler D M S & Whitt P R, *J org Chem*, **37** (1972) 4211.
- Tahara A, Shimaguchi M, Marigaya Y & Onada M, *Chem Lett*, (1974) 651.
- Settine R L & Gawish A A, *J org Chem*, **48** (1983) 2309.
- (a) Hewett C L, Gibson S G, Gilbert I M, Redpath J & Savage D S, *J chem Soc Perkin Trans-I*, (1973) 1967.
- (b) Hewett C L, Gilbert I M, Redpath J, Savage D S, Strachan J, Sleigh T & Taylor R, *J chem Soc Perkin Trans-I*, (1974) 897.
- (c) Hewett C L, Gibson S G, Redpath J & Savage D S, *J chem Soc Perkin Trans-I*, (1974) 1432.
- (d) Hewett C L, Gibson S G, Gilbert I L, Redpath J, Savage D S, Sleigh T & Taylor R, *J chem Soc Perkin Trans-I*, (1975) 336.
- (e) Campbell A C, Maidment M S, Pick J H, Stevenson D F M & Woods G F, *J chem Soc Perkin Trans-I*, (1978) 163.
- Birch A J & Subba Rao G S R, *Tetrahedron Lett*, (1967) 857.
- Windholz T B, Arison B, Brown R D & Patchett A A, *Tetrahedron Lett*, (1967) 3331.
- (a) Chatterjee A & Hazra B G, *Chem Commun*, (1970) 618.
- (b) Chatterjee A & Hazra B G, *Tetrahedron*, **36** (1980) 2513.
- (a) Chakraborty K K, Hazra B G & Gopichand Y, *Indian J Chem*, **12** (1974) 275.
- (b) Khanapure S P, Hazra B G & Das K G, *J chem Soc Perkin Trans-I*, (1981) 1360.
- Dalzell H C, Manmade A, Mastrocola A R & Razdan R K, *J org Chem*, **44** (1979) 2457.
- Schaeffe J, Ludwig B, Albrecht P & Ourisson G, *Tetrahedron Lett*, (1978) 4163 & references therein.
- Chatterjee A, Raychaudhuri S R & Chatterjee S K, *Chem Commun*, (1982) 24.
- French H E & Sears K, *J Am chem Soc*, **70** (1948) 1279.
- Friedman I & Schechter H, *J org Chem*, **26** (1961) 2522.
- Staskun B & Backeberg O G, *J chem Soc*, (1964) 5880.
- Kessar S V, Sobti A K & Joshi G S, *J chem Soc (C)*, (1971) 260.
- Williams J W, *Org Synth. Coll Vol III*, (1955) 626.
- Newman M S & Flanagan H R, *J org Chem*, **23** (1958) 796.
- Allen F H & Johnson H B, *Org Synth. Coll Vol II*, (1963) 804.
- House H O, Larson J K & Muller H C, *J org Chem*, **33** (1968) 961.
- Nal Cook P, *J org Chem*, **27** (1962) 3873.

- (b) Papa Domenick, Schwenk E & Whitman B, *J org Chem*, **7** (1942) 1587.
- 24 Brieger G & Fu T H, *Chem Commun*, (1976) 757.
- 25 Stork G & Schulenberg J W, *J Am chem Soc*, **84** (1962) 284.
- 26 Murphy J G, Ager J H & May E L, *J org Chem*, **25** (1960) 1386.
- 27 Jensen B L & Michand D P, *Synthesis*, (1977) 848.
- 28(a) Wenkert E & Stevens T E, *J Am chem Soc*, **78** (1956) 2318.
- (b) Meyer W L & Maheswari K K, *Tetrahedron Lett*, (1964) 2175.
- (c) Turner R B, Dianna G D, Foder G E, Gebert K, Simmons D L, Rao A S, Roos O & Wirth W, *J Am chem Soc*, **88** (1966) 1786.
- 29 Huffman J W & Charles J T, *J Am chem Soc*, **90** (1968) 6486.

## Base-induced Thermal Decomposition of Terpenoid Tosylhydrazones: Part I—Chemistry of Diazolongibornanes†

N SATYANARAYANA & U R NAYAK\*

National Chemical Laboratory, pune 411 008

Received 29 April 1985; accepted 24 June 1985

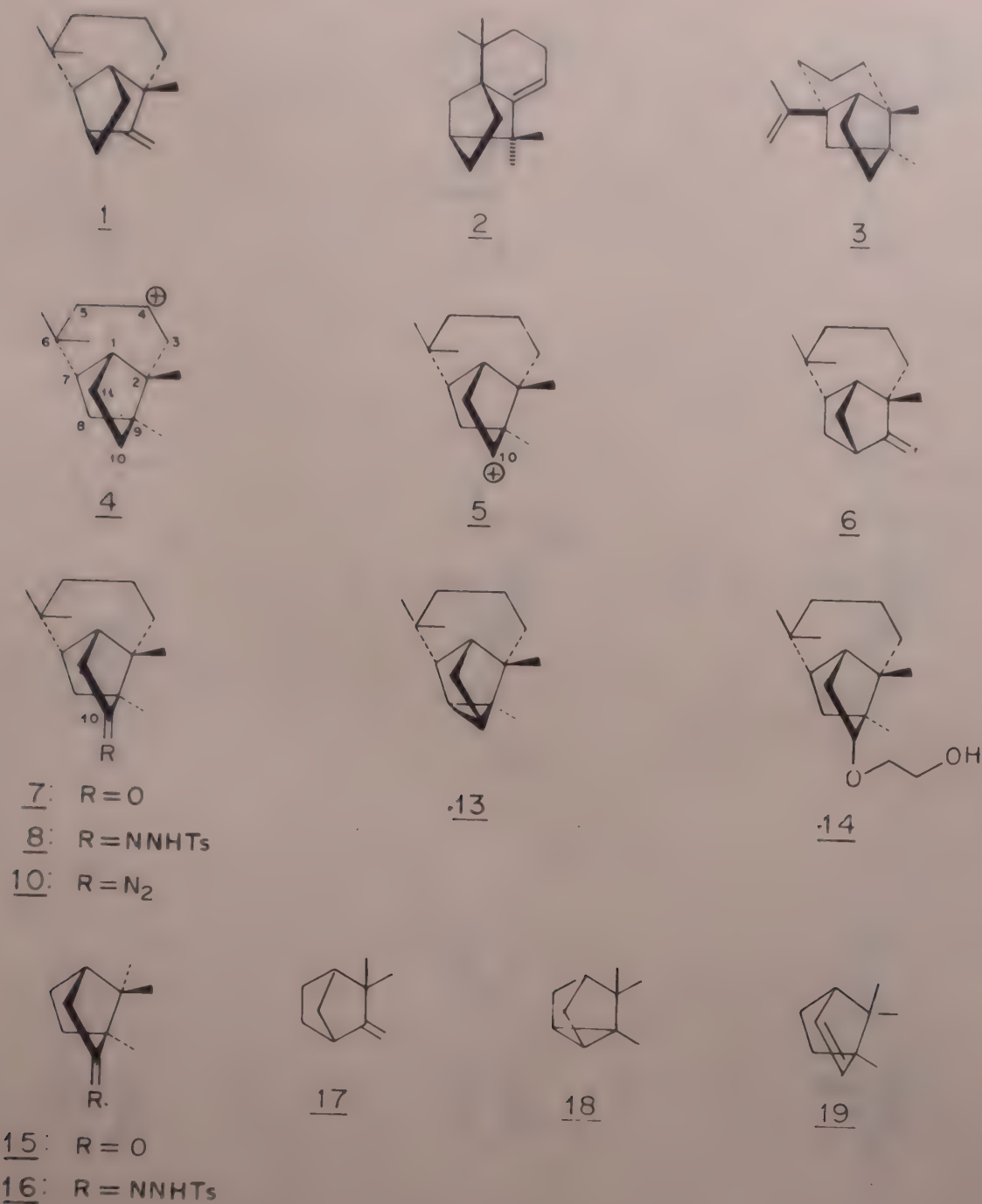
The elusive progenitor neolongifolene (**6**) of isolongifolene (**2**) has been synthesized (44% yield) from longicamphor tosylhydrazone (**8**) by generating the crucial longibornyl-10-cation (**5**) under basic conditions in a protic (sodium-ethylene glycol) Bamford-Stevens reaction; longicyclene (**13**, 15%) and the ether-carbinol (**14**, 16%) are the other products. Exposure of **6** to  $\text{BF}_3 \cdot \text{OEt}_2$  in benzene transforms it to **2**. Under aprotic conditions (sodium methoxide-diglyme) **8** gives longicyclene (**13**) as the major product (41%) with a trace (5%) of **6**. When **8** is exposed to *n*-butyllithium in hexane, the novel longibornylene (**21**) (54%) is formed. Generation of an electron-deficient species at the C-4 position on the longibornane skeleton via  $24 \rightarrow 25 \rightarrow 26$  (54%) has been studied: a novel transannular carbene insertion product **30** is formed from **24** under aprotic conditions only [ $\text{NaOMe}$ -diglyme, 16%; *t*-BuOK-diglyme, 26%]. In this reaction olefins **27** and **28** are very minor (<5%); the major crystalline compound is the 4-oxolongibornane azine (**31**) (~30%). Refluxing **24** in ethylene glycol with the sodium salt of ethylene glycol yields **27** (15%) and **28** (16%), besides the oxygenated compound **29** (19%).

A terpenic cation generated in a basic medium (intrinsically unfavourable for this species) can be expected, in principle, to give a simple alkene compared to the carbonium ion created in an acid medium which is quite conducive to deep-seated multiple rearrangements<sup>1</sup>. A classic example of the latter type is found in longifolene (**1**) which generates totally-transformed isomers, viz. isolongifolene (**2**)<sup>2</sup>/alloisolongifolene<sup>3</sup> (**3**) when exposed to specific acidic reagents. In the former context, we now describe the generation and study of the fate of two longibornane-based cations **4/5** in a basic reaction medium (Bamford-Stevens reaction<sup>4</sup>). Interestingly, this resulted in the formation of neolongifolene (**6**), the elusive intermediate in the acid-catalyzed rearrangement of **1** to **2**, the intermediacy of which could not be probed by the deuterium-labelling method<sup>5</sup>.

In essence, the problem consists in generating the crucial longibornyl-10-cation (**5**) under non-acidic conditions so that the camphane-based cation (**12**) (Scheme 1), arising from **5** by a Wagner-Meerwein 1,2-skeletal shift, stabilizes the proton elimination to **6** without undergoing further deep-seated rearrangement to **2**. As a possible solution, we generated 10-diazolongibornane (**10**) (Scheme 1) by refluxing the tosylhydrazone (**8**) of longicamphor<sup>6</sup> (**7**) with ethylene glycol, in which metallic sodium was dissolved, in a protic Bamford-Stevens reaction. Loss of nitrogen from longibornane-10-diazonium ion (**11**) created the key carbocation (**5**) (in a basic medium) which afforded at least 45% of the expected **6**, supported by IR bands at 3070, 1660, 890  $\text{cm}^{-1}$  and PMR at  $\delta$  4.76, 4.40 (two

singlets, 1H,  $>\text{C}=\text{CH}_2$ ), 2.72 (1H, *bs*, allylic CH) and  $1.12 \times 2, 0.84$  (three tertiary methyl singlets). The other two products formed in the reaction were separated by a combination of silica gel/ $\text{Ag}^+$ -impregnated silica gel chromatography and were readily characterized as longicyclene<sup>7</sup> (**13**) (15%; vide infra) and the ether-carbinol (**14**) (16%) resulting from alkylation of **5** with ethylene glycol. As anticipated, exposure of **6** to  $\text{BF}_3 \cdot \text{OEt}_2$  in benzene at ambient temperature smoothly transformed it to **2**.

In the history and development<sup>4</sup> of the Bamford-Stevens reaction, the tosylhydrazone (**16**) of camphor (**15**) (a bicyclo [2.2.1] heptane-based,  $\alpha$ -hydrogen bearing, bicyclic monoterpene ketone) under protic<sup>8</sup>, aprotic<sup>9</sup> and alkyllithium<sup>10</sup> conditions gave different products—camphene (**17**), cyclene (**18**) and bornylene (**19**) respectively. The importance of the Shapiro reaction<sup>11</sup> (alkyllithium variation) lies in that it enables the synthesis of difficultly accessible, unrearranged, less-substituted alkenes. Having studied the protic Bamford-Stevens reaction on the longi homologue **8** (a bicyclo [2.2.1] heptane-based,  $\alpha$ -hydrogen bearing, tricyclic sesquiterpene ketone derivative) of **16** with gratifying success, it was only logical to investigate the other two variations of the reaction also. When **8** was refluxed with sodium methoxide in diglyme (aprotic conditions), **13** was formed as the major hydrocarbon (44%) from the carbenic<sup>12</sup> intermediate (**20**) via an intramolecular insertion reaction; only a trace (5%) of **6** could be isolated. The Shapiro reaction (*n*-BuLi in hexane) on **8** gave a complex mixture from which only one olefin (54%) could be isolated pure. From spectral data [IR (smear): 3070, 1650, 760  $\text{cm}^{-1}$ . PMR:  $\delta$  6.05 (1H, *dd*,  $-\dot{\text{C}}\text{H}-\dot{\text{C}}\text{H}=\text{CH}-$ ,  $J_1=6\text{ Hz}$ ,  $J_2=4\text{ Hz}$ ); 5.61

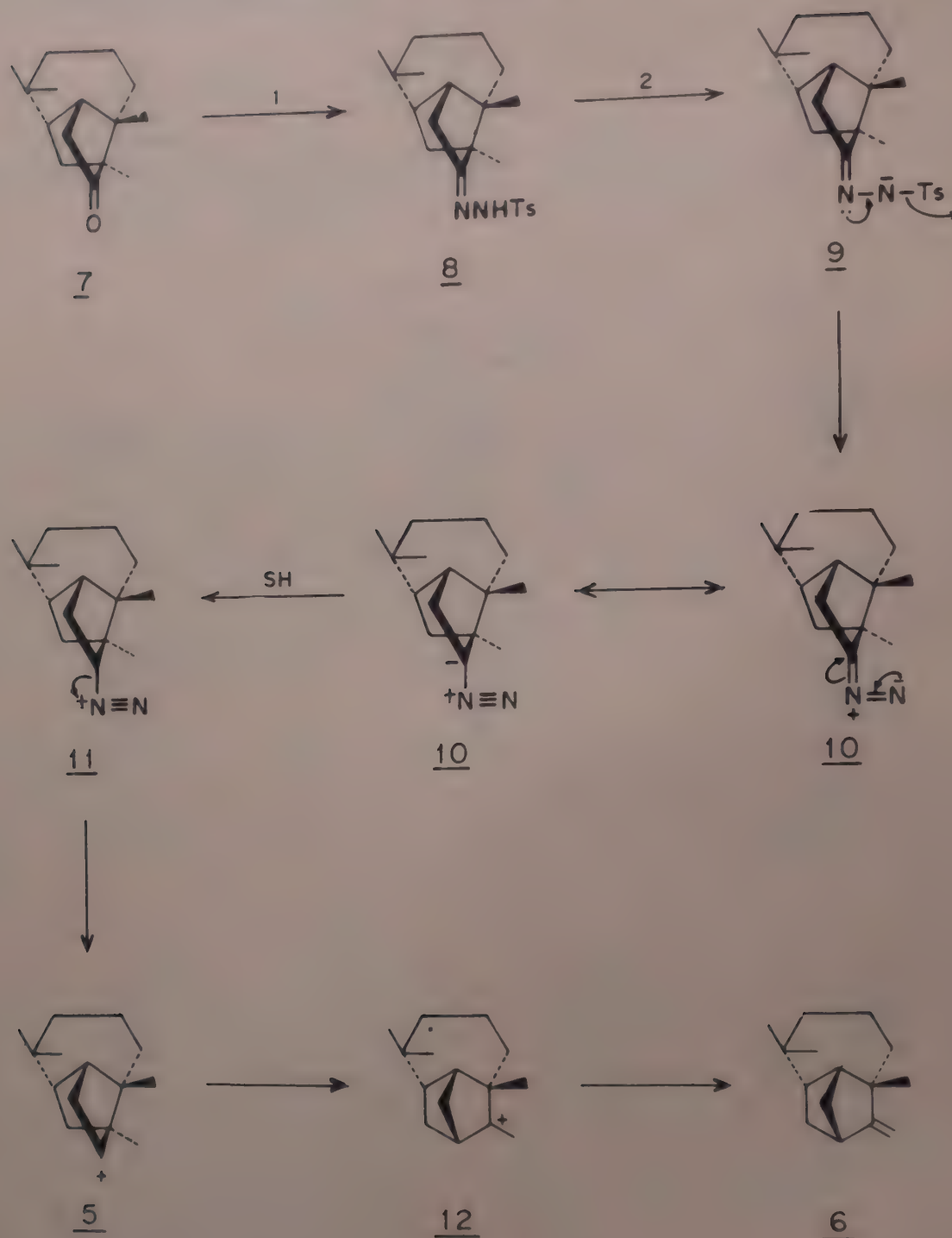


(*d*, 1H,  $-\text{CH}-\text{CH}=\text{CH}-$ ,  $J=6$  Hz); 1.03, 0.98, 0.87, 0.83 (four tertiary methyl singlets)] it was clearly the  $\alpha$ -hydrogen-eliminated, disubstituted olefinic longibornylene (21). It appears attractive to postulate the occurrence of 21 in nature (as yet not reported) since its progenitor longibornyl-10-cation (5) is easily derivable from longibornyl-8-cation [which is the immediate biogenetic<sup>13</sup> harbinger of longifolene (1)]; furthermore, the monoterpene counterpart of 21 namely bornylene (19) has been isolated long back from the essential oil of *Curcuma caesia*<sup>14</sup> Roxb.

There are three important longibornane-based ketones, of which 8-oxolongibornane (22) is highly hindered<sup>15</sup> and does not form any derivative. The other two ketones, 4-oxolongibornane (23) and 10-oxolongibornane (7) (longicamphor, already discussed above) are quite reactive and were synthesized from longifolene<sup>16</sup> and longicyclene<sup>6</sup> respectively.

Although acetic acid is the recommended solvent for preparation of crystalline tosylhydrazones of ketones, it is found that many longifolene-derived ketones do not give crystalline derivatives by this method. In such cases chloroform has proved much superior and afforded crystalline tosylhydrazones without much difficulty. It must however be mentioned here that while longicamphor tosylhydrazone (8) (AcOH method) was a single isomer, the tosylhydrazone (24) ( $\text{CHCl}_3$  method) was a mixture of *syn/anti* isomers (see Experimental).

In order to see whether any transannular<sup>5d</sup> rearrangement/insertion reaction was possible, an electron-deficient species was created at the spatially-strategic C-4 position on the longibornane skeleton (cationic 4/carbenic 26) by subjecting the tosylhydrazone (24) of 23 to the protic/aprotic Bamford-Stevens reaction conditions. When 24 was refluxed in ethylene



Reagents: 1.  $\text{TsNHNH}_2 - \text{AcOH}$  2.  $\text{Na} - (\text{CH}_2\text{OH})_2$

### SCHEME 1

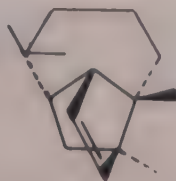
glycol with the sodium salt of ethylene glycol and the products isolated by a combination of silica gel  $\text{Ag}^+$ -impregnated silica gel chromatography, it gave the known olefins **27** (15%) and **28** (16%), formed by simple adjacent proton elimination, with no evidence of any 1,5-hydride shift; the oxygenated material consisted of the ether-carbinol (**29**) (19%).

A carbene insertion reaction, in a 1,5-transannular fashion, was however achieved when **24** was refluxed in diglyme with  $\text{NaOMe}$  (16%) or  $t\text{-BuOK}$  (26%). Chromatographic resolution ( $\text{Ag}^+$ -silica gel) of the hydrocarbon part gave a faster-moving, saturated

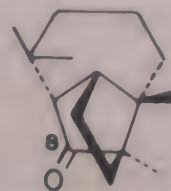
hydrocarbon (TNM test: negative; not longibornane<sup>18</sup>) for which the 4,8-cyclolongibornane structure (**30**) ( $M^+ 204$ ) has been assigned. Its PMR spectrum was characterized by four tertiary methyl singlets at  $\delta$  0.76, 0.84, 0.96, 1.08 and a transparent olefinic region; its IR spectrum was featureless while absence of any tetrasubstituted double bond was clear from the CMR of the compound. In either case, the olefins **27** and **28** were formed only in trace amounts (<5%) while the major product was a crystalline nitrogen-containing dimer (not formed in the case of **8**). That this compound ( $\text{C}_{30}\text{H}_{48}\text{N}_2$ ;  $M^+ 436$ ) was the 4-oxolongibornane azine



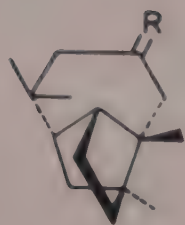
20



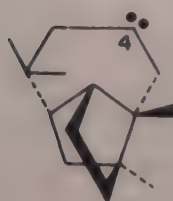
21



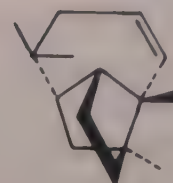
22



23 : R = O



26



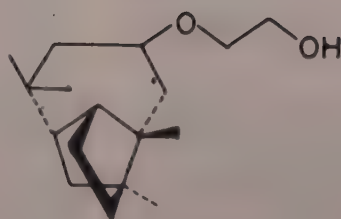
27

24 : R = NNHTs

25 : R = N<sub>2</sub>



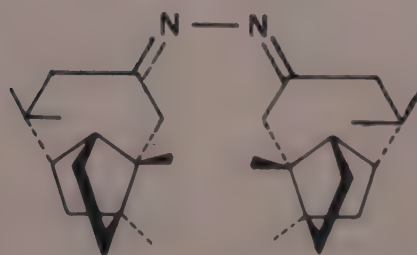
28



29



30



31

(31) was borne out from its spectral data (IR: strong band at 1630 cm<sup>-1</sup>).

#### Experimental Procedure

All m.ps. and b.ps. are uncorrected. Light petroleum refers to the fraction b.p. 60-80°. Solvent extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. IR spectra ( $\nu_{max}$  in cm<sup>-1</sup>) were recorded as smears (liquid) or nujol mulls (solid) on a Perkin-Elmer infracord model 137E or Pye Unicam SP-3 IR spectrophotometer, PMR spectra on

a Varian T60/FT 80A, CMR spectra on a Bruker WH-90 FT spectrometer and mass spectra (MS) on CEC 21-110B/AEI-MS30 spectrometers, using an ionizing voltage of 70 eV and a direct inlet system.

#### Longicamphor tosylhydrazide (8)

To a hot solution of longicamphor (7, 4.4 g) in AcOH (12 ml) was added a hot solution of tosylhydrazine (4 g) in AcOH (8 ml) and refluxed for 5 min. The mixture was cooled, the separated solid was filtered and

recrystallized from MeOH to afford colourless needles of **8** (4.8 g, 62 %) m.p. 176-78° (d); IR(nujol): 3045, 1665, 1600, 1170; PMR(CCl<sub>4</sub>):  $\delta$  7.60 (d, 2H, aromatic,  $J=8$  Hz), 7.03 (d, 2H, aromatic,  $J=8$  Hz), 2.37 (s, 3H, aromatic methyl), 0.93, 0.87, 0.70, 0.57 (four tertiary Me singlets) (Found: C, 67.9; H, 8.4; N, 7.7; S, 8.5. C<sub>22</sub>H<sub>32</sub>O<sub>2</sub>N<sub>2</sub>S requires C, 68.0; H, 8.3; N, 7.2; S, 8.2 %).

*Protic Bamford-Stevens reaction on 8:*

*Formation of neolongifolene (6), longicyclene (13) and ether-carbinol (14)*

Tosylhydrazone (**8**, 2 g) was added to a solution of metallic sodium (460 mg) in ethylene glycol (15 ml) and heated under reflux for 1 hr. The mixture was diluted with water, extracted with light petroleum (3  $\times$  50 ml), washed with brine, dried, the solvent removed and the residue chromatographed over SiO<sub>2</sub> gel (with TLC monitoring). Fr. 1, light petroleum, 2  $\times$  50 ml, 865 mg, mixture (AgNO<sub>3</sub>-TLC; 2 spots). Fr. 2, 10 % EtOAc-benzene, 3  $\times$  30 ml, pure, ether-carbinol (**14**) (epimeric mixture), colourless thick liquid, b.p. 135° (bath)/0.7 mm (220 mg, 16 %); IR (smear): 3440, 1120, 1080. PMR(CCl<sub>4</sub>):  $\delta$  3.53 (bm, 5H,  $-\dot{H}C-O-CH_2-CH_2-OH$ ), 0.76-1.30 (12H, 4 tertiary methyls each of two epimers) (Found: C, 76.5; H, 11.3. C<sub>17</sub>H<sub>30</sub>O<sub>2</sub> requires: C, 76.6; H, 11.4 %).

Fr. 1 was chromatographed over 15 % AgNO<sub>3</sub>-SiO<sub>2</sub> gel (with TLC monitoring): Fr. 1a, light petroleum (40 ml), longicyclene (**13**) (162 mg, 15 %) identified by IR/PMR. Fr. 1b, light petroleum (30 ml), mixture (42 mg). Fr. 1c, light petroleum (5  $\times$  40 ml), neolongifolene (**6**), b.p. 90° (bath)/0.7 mm (463 mg, 44 %); IR (smear): 3070, 1660, 890; PMR (CDCl<sub>3</sub>):  $\delta$  4.76, 4.40 (two singlets, 1H each,  $>C=CH_2$ ), 2.72 (1H, bs, allylic CH), 1.12  $\times$  2, 0.84 (three tertiary Me singlets). MS:  $m/z$  204 (M<sup>+</sup>) (Found: C, 88.4; H, 12.0. C<sub>15</sub>H<sub>24</sub> requires C, 88.2; H, 11.8 %).

*Action of BF<sub>3</sub>.OEt<sub>2</sub> on neolongifolene (6):*

*Formation of isolongifolene (2)*

**6** (77 mg) in dry benzene (5 ml) was cooled and treated with BF<sub>3</sub>.OEt<sub>2</sub> (one drop) and left at room temperature (18 hr). The mixture was diluted with benzene (30 ml), washed with aq. NaHCO<sub>3</sub>, brine, dried, solvent removed and the residue distilled to give **2** (58 mg, 75 %), identified by IR/PMR.

*Aprotic Bamford-Stevens reaction on 8:*

*Formation of 13 and 6*

**8** (2.14 mg) was added to a solution of NaOMe (1.15 mg) in dry MeOH (10 ml) and refluxed for 1 hr. The mixture was diluted with water (100 ml), extracted with light petroleum (3  $\times$  30 ml), washed with brine, dried, solvent removed and the residue chromatographed on 15 % AgNO<sub>3</sub>-SiO<sub>2</sub> gel (with TLC monitoring). Elution

with light petroleum (40 ml) gave a pure **13** (IR/PMR), b.p. 90° (bath)/2 mm (202 mg, 41 %). Further elution with light petroleum gave pure **6** (28 mg, 5 %).

*Action of n-BuLi on 8: Formation of longibornylene (21)*

*n*-Butyllithium (1.56 M, solution in hexane; 6.6 ml) was added to a stirred slurry of **8** (1 g) in dry ether (30 ml) under nitrogen. After the addition (10 min), the stirring was continued at room temperature for 3 hr, treated cautiously with water (30 ml) the ether layer separated and the aqueous layer extracted with ether (3  $\times$  30 ml). The combined ether extract was washed with brine, dried, solvent removed and the residue chromatographed on SiO<sub>2</sub> gel (with TLC monitoring). Fr. 1, light petroleum, 2  $\times$  30 ml, pure. Fr. 2, 50 % benzene-light petroleum, 5  $\times$  30 ml, complex mixture (348 mg).

Fr. 1 was distilled to furnish **21** as a colourless liquid, b.p. 90° (bath)/1.5 mm (286 mg, 54 %); IR (smear): 3070, 1650, 760; PMR (CCl<sub>4</sub>):  $\delta$  6.05 (dd, 1H,  $-\dot{C}H-CH=CH-$ ,  $J_1=6$  Hz,  $J_2=4$  Hz), 5.61 (d, 1H,  $-\dot{C}H-CH=CH-$ ,  $J=6$  Hz), 1.03, 0.98, 0.87, 0.83 (four tertiary Me singlets). MS:  $m/z$  204 (M<sup>+</sup>) (Found: C, 88.4; H, 12.0. C<sub>15</sub>H<sub>24</sub> requires C, 88.2; H, 11.8 %).

*4-Oxolongibornane tosylhydrazone (24)*

4-Oxolongibornane (**23**, 5 g) and tosylhydrazine (5.1 g) in CHCl<sub>3</sub> (100 ml) were refluxed on a water-bath (18 hr). The mixture was taken to dryness and the residue recrystallized from MeOH to yield (6 g, 68 %) **24** (syn/anti isomers) as white needles, m.p. 135-38° (d); (6 g, 68 %); IR (nujol): 3260, 1640, 1600, 1175, 820. PMR (CDCl<sub>3</sub>):  $\delta$  7.92 (d, 2H, aromatic,  $J=8$  Hz), 7.32 (d, 2H, aromatic,  $J=8$  Hz), 2.44 (s, 3H, aromatic methyl); 0.64-0.92 (a cluster of six singlets in this region) (Found: C, 68.2; H, 8.3; N, 7.6. C<sub>22</sub>H<sub>32</sub>O<sub>2</sub>N<sub>2</sub>S requires C, 68.0; H, 8.3; N, 7.2 %).

*Protic Bamford-Stevens reaction on 24:*

*Formation of olefins (27, 28) and ether-carbinol (29)*

**24** (2 g) was added to a solution of metallic sodium (460 mg) in ethylene glycol (15 ml) and refluxed for 1 hr. The mixture was worked up as described for **8** and the residue chromatographed on SiO<sub>2</sub> gel as before. Fr. 1, light petroleum, 4  $\times$  40 ml, 395 mg, mixture (AgNO<sub>3</sub>-TLC; 3 spots). Fr. 2, EtOAc, 2  $\times$  30 ml, pure ether-carbinol (**29**), which was obtained as colourless thick liquid, b.p. 140° (bath)/0.6 mm (266 mg, 19 %); IR (smear): 3440, 1110, 1070. PMR(CCl<sub>4</sub>):  $\delta$  3.50 (m, 5H,  $-\dot{C}H-O-CH_2-CH_2-OH$ ), 2.25 (bs, 1H,  $-\dot{O}H$ , exchanges with D<sub>2</sub>O), 1.00, 0.88  $\times$  2, 0.78 (four tertiary Me singlets). MS:  $m/z$  266 (M<sup>+</sup>), 204 (M - HO-CH<sub>2</sub>-CH<sub>2</sub>-OH, base peak) (Found: C, 77.0; H, 11.5. C<sub>17</sub>H<sub>30</sub>O<sub>2</sub> requires C, 76.6; H, 11.4 %).

Fr. 1 was chromatographed over 15 %  $\text{AgNO}_3\text{-SiO}_2$  gel as before. Fr. 1a, light petroleum (30 ml), olefin (27) (158 mg, 15 %) identified by IR/PMR. Fr. 1b, light petroleum (30 ml), mixture (45 mg). Fr. 1c, light petroleum ( $4 \times 20$  ml), olefin (28) (171 mg, 16 %) identified by IR/PMR.

#### Aprotic Bamford-Stevens reaction on 24

(with NaOMe): Formation of 27, 28, 4,8-cyclolongibornane (30) and 4-oxolongibornane azine (31)

24 (5 g) was refluxed (1 hr) in diglyme (50 ml) with NaOMe (1.4 g) and the product chromatographed on  $\text{SiO}_2$  gel. Fr. 1, light petroleum,  $2 \times 50$  ml, 730 mg, mixture ( $\text{AgNO}_3\text{-TLC}$ : 3 spots). Fr. 2, 50 % benzene-light petroleum,  $3 \times 40$  ml, mixture (400 mg). Fr. 3, EtOAc, 50 ml, pure solid, which was recrystallized from MeOH to afford white micro crystals of 31, m.p. 125-27° (943 mg, 34 %); IR (nujol): 1630; PMR ( $\text{CDCl}_3$ ):  $\delta$  1.04  $\times$  2, 0.92  $\times$  3, 0.88  $\times$  3 (eight tertiary Me singlets of the dimer 31); MS:  $m/z$  436 ( $M^+$ ) (Found: C, 82.1; H, 11.0; N, 6.4.  $\text{C}_{30}\text{H}_{48}\text{N}_2$  requires: C, 82.5; H, 11.1; N, 6.4 %).

Fr. 1 was chromatographed over 15 %  $\text{AgNO}_3\text{-SiO}_2$  gel as before. Fr. 1a, light petroleum ( $4 \times 30$  ml), 30, b.p. 90° (bath) 0.6 mm (427 mg, 16 %); IR(smear): transparent olefinic region; PMR( $\text{CDCl}_3$ ):  $\delta$  1.08, 0.96, 0.84, 0.76 (four tertiary Me singlets). CMR ( $\text{CDCl}_3$ ): No signal above 70 ppm; MS:  $m/z$  204 ( $M^+$ ). (Found: C, 87.94; H, 11.91.  $\text{C}_{15}\text{H}_{24}$  requires C, 88.2; H, 11.8 %). Fr. 1b, light petroleum ( $3 \times 25$  ml), olefin 27 (90 mg, 3 %) (IR/PMR). Fr. 1c, light petroleum ( $2 \times 30$  ml), mixture (107 mg). Fr. 1d, light petroleum ( $4 \times 30$  ml), olefin 28 (87 mg, 3 %) (IR/PMR).

#### References

- 1 Saunders M, Chandrasekhar J & Schleyer P V R in *Rearrangements in ground and excited states*, Vol. 1, edited by P de Mayo (Academic Press, New York) 1980, pp. 1-54.
- 2 (a) Prahlad J R, Ranganathan R, Nayak U R, Santhanakrishnan T S & Sukh Dev, *Tetrahedron Lett*, (1964) 417.  
(b) Ranganathan S, Nayak U R, Santhanakrishnan T S & Sukh Dev, *Tetrahedron*, **26** (1970) 621.
- 3 (a) Shitole H R, Vyas P & Nayak U R, *Tetrahedron Lett*, **24** (1983) 2411; *Indian J Chem*, **23B** (1984) 702.  
(b) Shitole H R, Dalavoy V S, Deodhar V B, Nayak U R, Acharya K R, Tavale S S, Guru Row T N, Kamat V P & Paknikar S K, *Tetrahedron Lett*, **24** (1983) 4739.
- 4 (a) Bamford W R & Stevens T S, *J chem Soc*, (1952) 4735.  
(b) Shapiro R H, *Organic Reactions*, **23** (1976) 405.  
(c) Casanova J & Waegall B, *Bull Soc chim Fr*, (1975) 922.
- 5 (a) Yadav J S, Nayak U R & Sukh Dev, *Tetrahedron*, **36** (1980) 309.  
(b) Yadav J S, Soman R, Sobti R R, Nayak U R & Sukh Dev, *Tetrahedron*, **36** (1980) 2105.  
(c) Sukh Dev, *Acc chem Res*, **14** (1981) 82.  
(d) Sukh Dev, *Prog Chem Org Nat Prod*, **40** (1981) 50.  
(e) Shitole H R & Nayak U R, *Indian J Chem*, **22B** (1983) 215.
- 6 Suryawanshi S N & Nayak U R, *Tetrahedron Lett*, (1977) 2619; *Indian J Chem*, **19B** (1980) 1.
- 7 Nayak U R & Sukh Dev, *Tetrahedron Lett*, (1963) 243; *Tetrahedron*, **24** (1968) 4099.
- 8 Powell J W & Whiting M C, *Tetrahedron*, **7** (1959) 305.
- 9 Friedman L & Shechter, *J Am chem Soc*, **81** (1959) 5512.
- 10 Shapiro R H & Heath M J, *J Am chem Soc*, **89** (1967) 5734.
- 11 Adlington R M & Barrett G M, *Acc chem Res*, **16** (1983) 55.
- 12 (a) Kirmse W, *Carbene chemistry* (Academic press, New York), 1971, pp. 29-34.  
(b) Baron W J, DeCamp M R, Hendrick M E, Jones M (Jr), Levin R H & Sohn M B, *Carbenes*, Vol. 1, edited by M Jones (Jr.) & Moss R A (Wiley-Interscience, New York), 1973, pp. 1-151.
- 13 Manitto P, *Biosynthesis of natural products* (Ellis Horwood Ltd, Chichester), 1981, 246.
- 14 Dutt S, *Indian Soap J*, **6** (1940) 248; *Chem Abstr*, **34** (1940) 6015.
- 15 Naffa P & Ourisson G, *Bull Soc chim Fr*, (1954) 1115.
- 16 Nayak U R & Sukh Dev, *Tetrahedron*, **8** (1960) 42.
- 17 Gokhale P D, Joshi A P, Sahani R, Naik V G, Damodaran N P, Nayak U R & Sukh Dev, *Tetrahedron*, **32** (1976) 1391.
- 18 Prahlad J R, Nayak U R & Sukh Dev, *Tetrahedron*, **26** (1970) 66.

## Base-induced Thermal Decomposition of Terpenoid Tosylhydrazones: Part II—Chemistry of 8-Diazoisolongifolane/9-Diazoisolongifolene†

N SATYANARAYANA & U R NAYAK\*

National Chemical Laboratory, Pune 411 008

Received 8 May 1985; accepted 3 June 1985

7 $\alpha$ H-8-Oxoisolongifolane (3) on refluxing with tosylhydrazine in  $\text{CHCl}_3$  gives the tosylhydrazone (7) of the more stable epimer 7 $\beta$ H-8-oxoisolongifolane (6). Refluxing 7 with NaOMe in diglyme gives the disubstituted olefin (15, 31%), isolongifolene (2, 23%) and the unusual alcohol (16, 7%). Two pure C-8 epimers of the 2-hydroxyethyl ether 17 (27%) / 18 (6%) are formed in the protic Bamford-Stevens reaction (Na in ethylene glycol) on 7; isolongifolene (2, 20%) and 15 (13%) are the other products. Attempted preparation of the tosylhydrazone (10) from 8-oxoisolongifol-9-ene (9) generates only the saturated tosylhydrazone (7) via a concomitant reduction of the olefinic bond in 9 during the reaction. 9-Diazoisolongifolene (14) generated from the tosylhydrazone (13) under aprotic conditions gives the vinylcarbene-derived olefinic methyl ether epimers (20, 21) in a major yield (47%) while the diene (19, 6%) and the crystalline azine (22, 4%) are also formed. Refluxing 13 with Na in ethylene glycol generates the C-9 ethylene glycol substituted compound (23) (54%) with only a trace (4%) of 19.

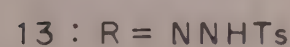
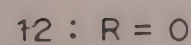
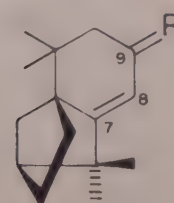
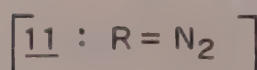
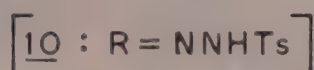
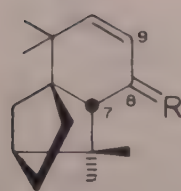
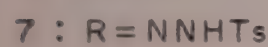
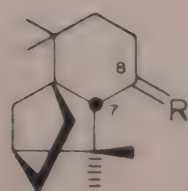
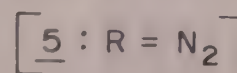
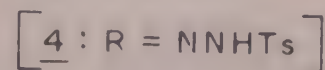
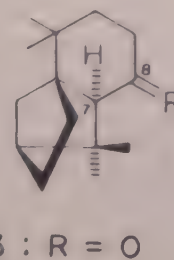
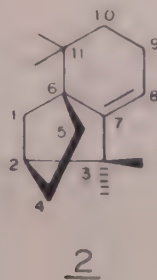
As part of our study dealing with the base-induced thermal decomposition of tosylhydrazones of ketones derived from longifolene (1) and its acid-catalyzed isomers, we earlier described<sup>1</sup> the chemistry of two diazolongibornanes resulting in the synthesis<sup>1</sup> of neolongifolene—the elusive precursor of isolongifolene (2). The preparation of tosylhydrazones from saturated/ $\alpha,\beta$ -unsaturated ketones derived from 2 and a comparative study of the Bamford-Stevens reaction<sup>2</sup> (protic/aprotic conditions) on these substrates forms the subject of this paper.

The fate of the intermediate diazo compound, generated from the tosylhydrazone of a saturated/ $\alpha,\beta$ -unsaturated ketone, in a Bamford-Stevens reaction<sup>2</sup>, is largely dependent on the nature of the solvent. In aprotic medium molecular nitrogen is eliminated and a carbene/vinylcarbene is generated. In protic medium a diazonium ion is formed. This diazonium ion can lose nitrogen giving a carbonium ion, which expels a proton with or without prior rearrangement. In order to study the fate of isolongifolane-based carbene/vinylcarbene intermediates we have now generated 8-diazoisolongifolane (8) 9-diazoisolongifolene (14) as precursors in an aprotic medium (NaOMe-diglyme). Since protic solvents frequently gives rise to totally different products, the reaction has also been investigated using metallic sodium dissolved in ethylene glycol.

Theoretically, two 8-diazoisolongifolanes, namely 7 $\alpha$ H (5) 7 $\beta$ H (8) arising from the tosylhydrazones 4/7

derived from ketones<sup>3</sup> 3/6, were possible but in practice only the 7 $\alpha$ H-8-diazoisolongifolane (8) could be generated. Attempted preparation of the 7 $\alpha$ H-tosylhydrazone (4) by refluxing 7 $\alpha$ H-8-oxoisolongifolane (3) with tosylhydrazine in chloroform gave the tosylhydrazone (7) of 7 $\beta$ H-ketone (6) (PMR: single geometrical isomer), as a result of initial epimerization of the C-7 centre in 3 during the reaction.

Refluxing 7 with sodium methoxide in diglyme and separating the reaction mixture by a combination of chromatography on silica gel/Ag<sup>+</sup> silica gel gave the disubstituted olefin (15) (31%) / isolongifolene (2) (23%) via hydride migration to the carbene<sup>4</sup>, and a meagre yield of the rather unusual secondary alcohol<sup>5</sup> (16) (7%). [The carbinol (16) (liquid) is the epimer of the 8 $\beta$ -(equatorial)hydroxyisolongifolane (crystalline) obtained<sup>3</sup> by Na-PrOH reduction 6]. Mechanistically formation of 16 can be rationalized<sup>5</sup> via hydrolysis of the ester resulting from attack of toluene sulfinate anion (expelled from 7) on the carbocation derived from the diazonium ion (protonated diazo compound 8) after loss of nitrogen. In contrast, base-induced decomposition of 7 in protic ethylene glycol resulted in the formation of a sizable amount (33%) of oxygenated material (ethylene glycol substitution<sup>6</sup>) which on chromatography gave two pure C-8 epimers of the 2-hydroxyethyl ether 17 (27%) / 18 (6%). The  $\beta$ -equatorial orientation for the bulky substituent at C-8 as shown in 17 is based purely on stability considerations (equatorial versus axial) of the alkoxy group in 17 since no clear-cut PMR evidence ( $-\text{CH}-\text{OCH}_2\text{CH}_2\text{OH}$ ) could be deciphered from the complex multiplicity



pattern between  $\delta$  3.0 and 4.0. From the hydrocarbon part of the reaction mixture, the olefin **15** (13%)-isolongifolene (**2**) (20%) were isolated and characterized.

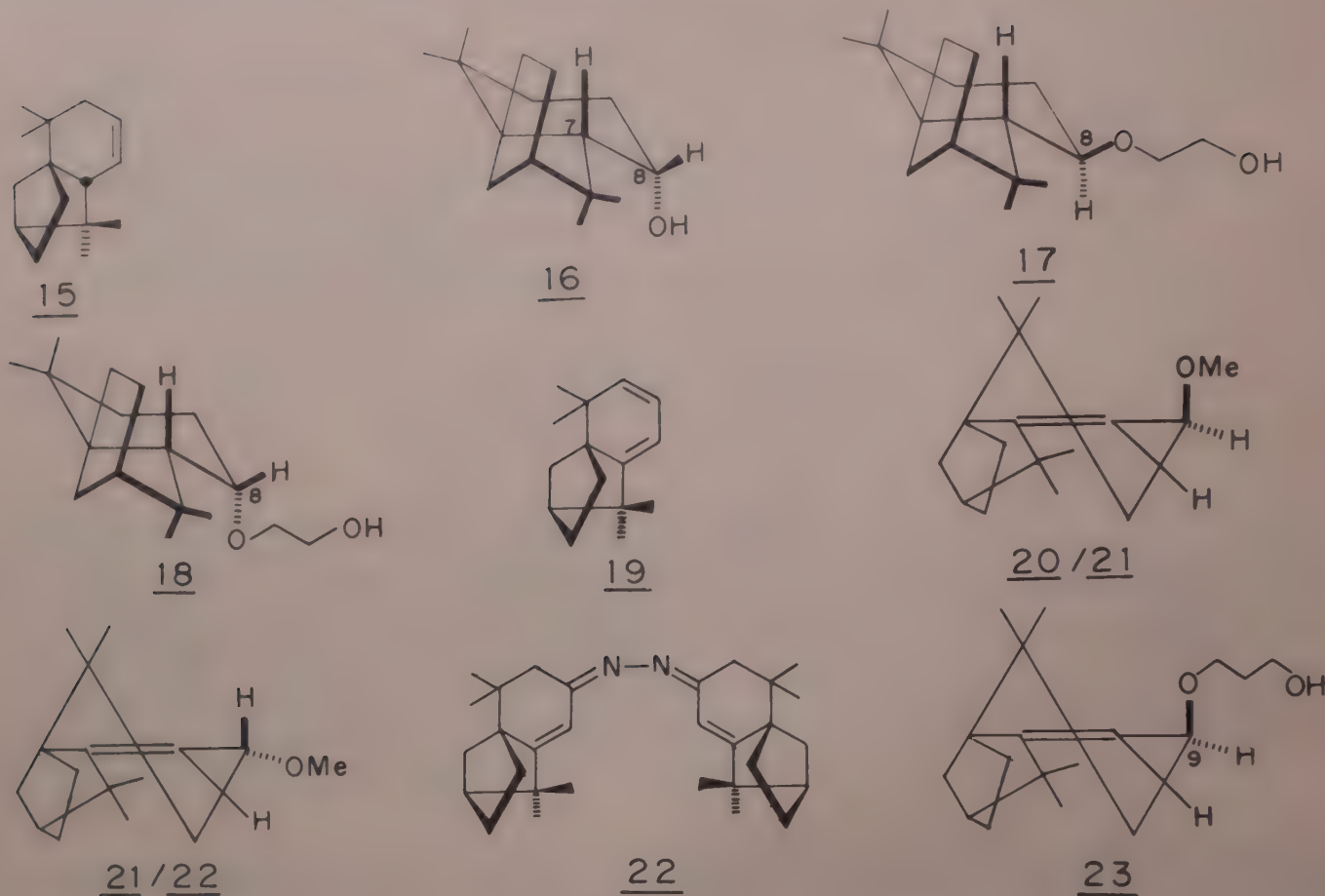
In order to study the chemistry of the related vinylcarbene<sup>7</sup> from 8-diazoisolongifol-9-ene (**11**) we needed the tosylhydrazone (**10**) but all our attempts to prepare it were in vain. The conjugated ketone **9**, readily accessible from **6**<sup>8</sup>, did not give the tosylhydrazone when refluxed with tosylhydrazine in chloroform<sup>1</sup>. Boiling **9** in acetic acid with tosylhydrazine, however, yielded a saturated tosylhydrazone identical with **7**; reduction of double bond during attempted preparation of the tosylhydrazone of a conjugated ketone has been reported<sup>9</sup> recently.

In sharp contrast to the behaviour of **9**, the isomeric enone **12** readily furnished the tosylhydrazone (**13**) (PMR: single geometrical isomer) by the chloroform method<sup>1</sup>. The fate of the vinylcarbene formed by loss of nitrogen from 9-diazoisolongifolene (**14**) generated by thermal decomposition of **13** under aprotic (NaOMe-diglyme) conditions was then studied. The formation of the methyl ethers<sup>11</sup> **20/21** (epimeric mixture; 47%) suggests that the methanol of neutralization formed in the reaction of **13** with NaOMe reacts with **14** to generate the observed products via the diazonium ion/nitrogen expulsion. Although the mixture of olefinic methyl esters could be separated (chromatography on Ag<sup>+</sup> silica gel) to

afford the two pure epimers **20/21**, it was not possible to make unambiguous assignment of their configurations on the basis of their PMR spectra (=CH-CHOME). Two other minor products separated from the reaction mixture were characterized as the 1,3-diene<sup>10</sup> (**19**) (6%) and the crystalline azine (**22**) (4%) on the basis of their spectral data. Finally, when **13** was subjected to protic Bamford-Stevens conditions (Na in ethylene glycol), an oxygenated product was formed in major yield (54%). From its spectral data it was clearly the C-9 ethylene glycol substituted compound **23** and from its PMR appeared to be a single epimer; in the cyclohexene ring of **23**, the bulky group on the carbon adjacent to the double bond has been shown with the slightly less hindered preferred axial orientation. The only other pure compound separated from the reaction mixture in this case was the diene (**19**) (4%).

### Experimental Procedure

All m.ps. and b.ps. are uncorrected. Light petroleum refers to the fraction b.p. 60-80°. Solvent extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. IR spectra ( $\nu_{\max}$  in cm<sup>-1</sup>) were recorded as smears (liquid) or nujol mulls (solid) on a Pye-Unicam SP-3 IR spectrophotometer, PMR spectra Varian T60/FT80A spectrometers and mass spectra (MS) on a CEC spectrometer model 21-110B, using an ionizing voltage of 70eV and a direct inlet system.



#### 7 $\beta$ H-8-Oxoisolongifolane tosylhydrazone (7)

Ketone (6, 6 g) and tosylhydrazine (6.1 g) in  $\text{CHCl}_3$  (60 ml) were refluxed on a water-bath (18 hr). The mixture was taken to dryness and the residue recrystallized from MeOH to yield 7 as colourless needles, m.p. 142–45° (d) (8.9 g, 84%); IR (nujol): 3250, 1600, 1175, 820; PMR ( $\text{CDCl}_3$ ):  $\delta$  7.88 (d, 2H, aromatic,  $J=8$  Hz); 7.28 (d, 2H, aromatic,  $J=8$  Hz); 2.48 (s, 3H, aromatic methyl); 1.04, 0.92, 0.80, 0.40 (four tertiary Me singlets); MS:  $m/z$  388 ( $\text{M}^+$ ); 233 ( $\text{M} - \text{SO}_2\text{C}_6\text{H}_4\text{-p-CH}_3$ , base peak). (Found: C, 68.0; H, 8.2; N, 7.8; S, 8.8.  $\text{C}_{22}\text{H}_{32}\text{O}_2\text{N}_2\text{S}$  requires C, 68.0; H, 8.3; N, 7.2; S, 8.2%).

#### Aprotic Bamford-Stevens reaction on 7: Formation of isolongifolene (2), olefin (15) and alcohol (16)

Tosylhydrazone (7, 2.5 g) was added to a solution of NaOMe (1.4 g) in diglyme (25 ml) and refluxed for 1 hr. The mixture was quenched in cold water (125 ml), extracted with light petroleum (3  $\times$  50 ml), washed with brine, dried, solvent removed and the residue chromatographed on  $\text{SiO}_2$  gel (with TLC monitoring): Fr. 1, light petroleum, 2  $\times$  40 ml, 723 mg, mixture ( $\text{AgNO}_3$ -TLC; 2 spots). Fr. 2, light petroleum, 40 ml, 56 mg, mixture. Fr. 3, 50% benzene-light petroleum, 35 ml, pure 16, colourless thick liquid, b.p. 140° (bath) 0.8 mm (113 mg, 7%). IR (smear): 3520, 1100, 1045. PMR ( $\text{CDCl}_3$ ):  $\delta$  4.08 (s, 1H,  $-\text{CH}-\text{OH}$ ); 1.20, 1.00, 0.88  $\times$  2 (four tertiary Me singlets). MS:  $m/z$  222 ( $\text{M}^+$ ).

Fr. 1 was chromatographed over 15%  $\text{AgNO}_3\text{-SiO}_2$  gel (with TLC monitoring): Fr. 1a, light petroleum, 2  $\times$  15 ml, pure isolongifolene (2) (306 mg, 23%) identified by IR/PMR. Fr. 1b, light petroleum, 15 ml (59 mg). Fr. 1c, light petroleum, 4  $\times$  15 ml, pure 15, colourless liquid, b.p. 95° (bath)/0.8 mm (400 mg, 31%); IR (smear): 3030, 1660, 680. PMR ( $\text{CDCl}_3$ ):  $\delta$  5.56 [degenerate AB "quartet" ( $\delta/J$  very small), 2H,  $-\text{CH}=\text{CH}-$ ]; 1.04, 0.92, 0.88, 0.84 (four tertiary Me singlets). MS:  $m/z$  204 ( $\text{M}^+$ ) (Found: C, 88.4; H, 12.0.  $\text{C}_{15}\text{H}_{24}$  requires C, 88.2; H, 11.8%).

#### Protic Bamford-Stevens reaction on 7: Formation of 2, 15 and 2-hydroxyethyl ethers (17/18)

Tosylhydrazone (7, 2.5 g) was added to a solution of metallic sodium (607 mg) in ethylene glycol (25 ml) and refluxed for 1 hr. The mixture was quenched in cold water, extracted with light petroleum (3  $\times$  60 ml), washed with brine, dried, the solvent removed and the residue chromatographed over  $\text{SiO}_2$  gel (with TLC monitoring): Fr. 1, light petroleum, 2  $\times$  40 ml, 564 mg, mixture ( $\text{AgNO}_3$ -TLC: 2 spots). Fr. 2, 1°, EtOAc-benzene, 2  $\times$  30 ml, pure. Fr. 3, 2°, EtOAc-benzene, 2  $\times$  30 ml, pure.

Fr. 2 was distilled to furnish 18 as a thick colourless liquid, b.p. 150° (bath) 0.5 mm (98 mg, 6%); IR (smear): 3400, 1115, 1070. PMR ( $\text{CDCl}_3$ ):  $\delta$  3.16–3.80 (m, 5H,  $-\text{CH}-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH}$ ); 1.08, 0.96, 0.88  $\times$  2 (four tertiary Me singlets); MS:  $m/z$  266 ( $\text{M}^+$ ) (Found: C, 76.7; H, 11.2.  $\text{C}_{17}\text{H}_{30}\text{O}_2$  requires C, 76.6; H, 11.4%).

Fr. 3 was distilled to give 17 as thick colourless liquid, b.p. 155° (bath)/0.5 mm (460 mg, 27%); IR (smear): 3460, 1120, 1055. PMR (CDCl<sub>3</sub>):  $\delta$  3.08-3.80 (m, 5H,  $-\overset{|}{\text{C}}\text{H}-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH}$ ); 1.08  $\times$  2, 0.88, 0.84 (four tertiary Me singlets). MS:  $m/z$  266 (M<sup>+</sup>, base peak).

Fr. 1 was chromatographed over 15% AgNO<sub>3</sub>-SiO<sub>2</sub> gel as before. Fr. 1a, light petroleum (5  $\times$  25 ml), isolongifolene (2) (273 mg, 20%) identified by IR/PMR. Fr. 1b, light petroleum (3  $\times$  25 ml), mixture (111 mg). Fr. 1c, light petroleum (4  $\times$  20 ml), disubstituted olefin 15 (180 mg, 13%) identified by IR/PMR.

#### Attempted preparation of tosylhydrazone 10: Formation of 7

To a hot solution of 9 (5.9 g) in AcOH (6 ml) was added a hot solution of tosylhydrazine (6.1 g) in AcOH (7 ml) and refluxed for 5 min. The mixture was cooled, the separated solid was filtered and recrystallized from MeOH when the saturated derivative, identical (m.m.p. IR/PMR) with 7 (6 g, 56%) was obtained.

#### 9-Oxoisolongifol-7-ene tosylhydrazone (13)

The conjugated ketone (12, 7 g) and tosylhydrazine (7.2 g) in CHCl<sub>3</sub> (70 ml) were refluxed (18 hr) and the residue obtained after usual work-up recrystallized from MeOH to yield white crystalline 13, m.p. 77-80° (d) (10.6 g, 85%); IR (nujol): 3500, 1645, 1600, 1175, 1040, 825; PMR (CDCl<sub>3</sub>):  $\delta$  7.92 (d, 2H, aromatic,  $J$  = 8 Hz); 7.40 (d, 2H, aromatic,  $J$  = 8 Hz); 5.82 (s, 1H, olefinic), 2.44 (s, 3H, aromatic methyl); 1.08, 1.04, 1.00, 0.84 (four tertiary Me singlets) (Found: C, 68.1; H, 8.1; N, 7.0; S, 8.1. C<sub>22</sub>H<sub>30</sub>O<sub>2</sub>N<sub>2</sub>S requires C, 68.4; H, 7.8; N, 7.3; S, 8.3%).

#### Aprotic Bamford-Stevens reaction on 13: Formation of diene (19), epimeric methyl ethers (20/21) and azine (22)

Tosylhydrazone (13, 3 g) was refluxed (1 hr) in diglyme (30 ml) with NaOMe (1.7 g). The mixture was worked-up as usual and the crude product chromatographed on SiO<sub>2</sub> gel. Fr. 1, light petroleum, 30 ml, pure (100 mg, 6%, diene 19, IR/PMR). Fr. 2, light petroleum, 4  $\times$  30 ml, mixture (851 mg, AgNO<sub>3</sub>-TLC; 2 spots). Fr. 3, 5% EtOAc, 30 ml, pure solid.

Fr. 3 was recrystallized from light petroleum to furnish yellow micro crystals of 22, m.p. 237-40° (68 mg, 4%); IR (nujol): 1640, 1580; PMR (CDCl<sub>3</sub>):  $\delta$  6.00 [s, 2H ( $>\text{C}=\text{CH}-\overset{|}{\text{C}}=\text{N}-$ )<sub>2</sub>]; 1.16  $\times$  2; 1.12  $\times$  2; 1.08  $\times$  2; 0.92  $\times$  2 (eight tertiary Me singlets) (Found: C, 83.2; H, 10.5; N, 6.1. C<sub>30</sub>H<sub>44</sub>N<sub>2</sub> requires C, 83.3; H, 10.3; N, 6.5%).

Fr. 2 was chromatographed over 15% AgNO<sub>3</sub>-SiO<sub>2</sub> gel as before. Fr. 1a, 25% benzene-light petroleum (3  $\times$  20 ml), methyl ether 20/21, b.p. 110° (bath)/1.5 mm (297 mg, 16%); IR (smear): 1680, 1100, 1080, 935; PMR

(CDCl<sub>3</sub>):  $\delta$  5.44 (d, 1H, olefinic,  $J$  = 5 Hz); 3.44-3.80 (m, 1H,  $-\overset{|}{\text{C}}\text{H}-\text{OCH}_3$ ); 3.36 (s, 3H,  $-\text{OCH}_3$ ); 1.08, 1.00, 0.96, 0.92 (four tertiary Me singlets) (Found: C, 82.5; H, 11.3. C<sub>16</sub>H<sub>26</sub>O requires C, 82.0; H, 11.2%). Fr. 1b, 25% benzene-light petroleum (2  $\times$  15 ml), methyl ether 21/20: b.p. 110° (bath)/1.5 mm (379 mg, 20%). IR (nujol): 1680, 1120. PMR (CDCl<sub>3</sub>):  $\delta$  5.32 (bs, 1H, olefinic); 3.76-4.00 (m, 1H,  $\overset{|}{\text{C}}\text{H}-\text{OCH}_3$ ); 3.40 (s, 3H,  $-\text{OCH}_3$ ); 1.08, 1.00, 0.96, 0.88 (four tertiary Me singlets). MS:  $m/z$  234 (M<sup>+</sup>, base peak). (Found: C, 82.1; H, 11.3. C<sub>16</sub>H<sub>26</sub>O requires; C, 82.0; H, 11.2%).

#### Protic Bamford-Stevens reaction on 13: Formation of diene (19) and 2-hydroxyethyl ether (23)

Tosylhydrazone (13, 3 g) was added to a solution of metallic sodium (0.7 g) in ethylene glycol (20 ml) and refluxed for 1 hr. The mixture was worked up as described for 7 and the residue chromatographed on SiO<sub>2</sub> gel (with TLC monitoring). Fr. 1, light petroleum, 40 ml, pure (69 mg, diene 19, IR/PMR). Fr. 2, 2% EtOAc-benzene, 2  $\times$  30 ml, 200 mg, mixture. Fr. 3, 5% EtOAc-benzene, 4  $\times$  25 ml, pure.

Fr. 3 was distilled to furnish 23 as a colourless thick liquid, b.p. 185° (bath)/4 mm (1.1 g, 54%); IR (smear): 3450, 1670, 1120, 1065; PMR (CDCl<sub>3</sub>)  $\delta$  5.30 (bs, 1H, olefinic); 3.48-4.16 (m, 5H,  $-\overset{|}{\text{C}}\text{H}-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH}$ ); 2.08 (bs, 1H,  $-\text{OH}$ , exchangeable with D<sub>2</sub>O); 1.08, 1.00, 0.96, 0.88 (four tertiary Me singlet) (Found: C, 76.7; H, 10.8. C<sub>17</sub>H<sub>28</sub>O<sub>2</sub> requires C, 77.2; H, 10.7%).

#### References

- 1 Satyanarayana N & Nayak U R, *Indian J Chem*, **25B** (1986) 22.
- 2 a) Bamford W R & Stevens T S, *J chem Soc*, (1952) 4735.  
b) Shapiro R H, *Organic Reactions*, **23** (1976) 405.  
c) Casanova J & Waegell B, *Bull Soc chim Fr*, (1975) 922.
- 3 Goudgaon N M & Nayak U R, *Indian J Chem*, (In press).
- 4 a) Kirmse W, *Carbene chemistry*, (Academic Press, New York) 1971, pp 29-34.  
b) Baron W J, DeCamp M R, Hendrick M E, Jones M (Jr), Levin R H & Sohn M B, *Carbenes*, Vol I, edited by M Jones (Jr) & R A Moss (Wiley-Interscience, New York) 1973, pp 1-151.
- 5 Wilst J W, Schneider C A, Dabek H F, Kraemer J F & Wagner W J, *J org Chem*, **31** (1966) 1543.
- 6 Paquette L A & Birnberg G H, *J Am chem Soc*, **94** (1962) 164.
- 7 Hartzler H D, in *Carbenes*, Vol II, edited by R A Moss & M Jones (Jr) (Wiley-Interscience, New York) 1975, pp 43-100.
- 8 Goudgaon N M & Nayak U R, *Indian J Chem*, (In press).
- 9 Jagodzinski J J & Siciński R R, *Tetrahedron Lett*, (1982) 1837.
- 10 Ranganathan R, Nayak U R, Santhanakrishnan T S & Sukh Dev, *Tetrahedron*, **26** (1970) 621.
- 11 a) Freeman P K, Ziebarth T D & Rao V N M, *J org Chem*, **38** (1973) 3823.  
b) Freeman P K, Raghavan B S & Kuper D G, *J Am chem Soc*, **93** (1971) 5288.  
c) Kirmse W & Ruetz L, *Liebigs Ann*, **726** (1969) 30.  
d) Findlay R H, Sharp J T & Thorogood P B, *Chem Commun*, (1970) 909.

## Base-induced Thermal Decomposition of Terpenoid Tosylhydrazones: Part III—Chemistry of 12-Diazoalloisolongifolane/12-Methyl- 12-diazoalloisolongifolane†

N SATYANARAYANA & U R NAYAK\*

National Chemical Laboratory, Pune 411 008

Received 6 June 1985; accepted 26 June 1985

The base-catalyzed thermal decomposition of tosylhydrazones (9/12) derived from the aldehyde (8) ketone (11) (generated from alloisolongifolene 1) has been studied. Under aprotic conditions (NaOMe in diglyme), 12-diazoalloisolongifolane (10) generates alloisolongifolene (1) (30%) and the cyclopropane derivative (17) (9%) while sodium in ethylene glycol gives 1 (54%) and the 2-hydroxyethyl ether (18) (24%). When the tosylhydrazone (12) is refluxed with NaOMe in diglyme, at least 2% of the 1,3-insertion product (20) is isolated along with the olefin (19) (42%); under protic conditions, 19 (20%), 20 (5%) and 2-hydroxyethyl ether (21) (8%) are formed.

As part of our study dealing with the base-induced thermal decomposition of tosylhydrazones of ketones derived from longifolene and its acid-catalyzed isomers, we have earlier described the chemistry of two diazolongibornanes<sup>1</sup> and 8-diazoisolongifolane<sup>2</sup>/9-diazoisolongifolene<sup>2</sup>. This paper deals with the generation and study of the fate of two acyclic monoalkyl/dialkyl diazo compounds derived from alloisolongifolene<sup>3</sup> (1).

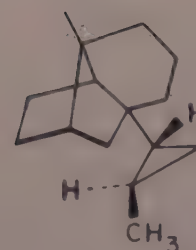
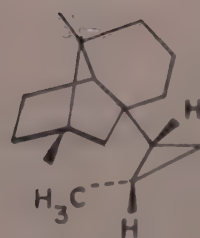
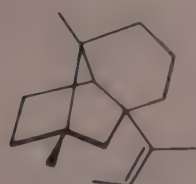
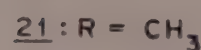
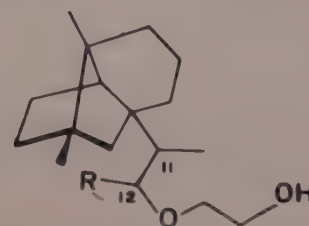
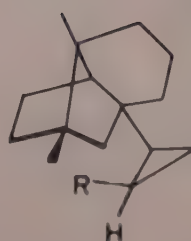
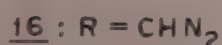
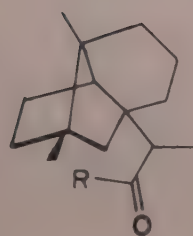
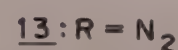
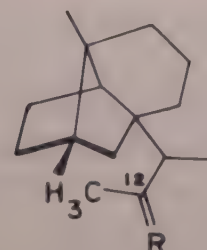
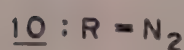
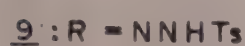
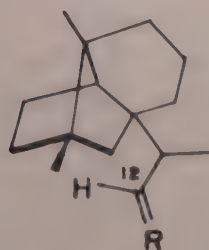
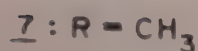
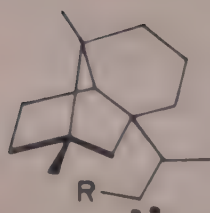
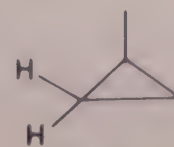
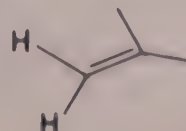
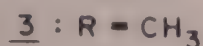
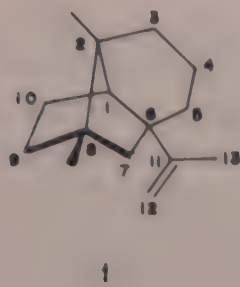
Typical of the behaviour of branched alkylcarbenes<sup>4</sup> are the reactions of isopropylcarbene (2). In this case, hydrogen shift to olefin 4 occurs<sup>5</sup> roughly twelve times as fast as insertion to give the cyclopropane (5). In order to find out the relative ease of 1,2 and 1,3 carbon-hydrogen insertion in monoalkyl/dialkyl carbenes of the type 2/3 incorporated as part of a complex bridged system exemplified by 6/7, we have studied the base-catalyzed thermal decomposition of tosylhydrazones (9/12) derived from the aldehyde (8)/ketone (11) (aprotic/protic Bamford-Stevens reaction<sup>6</sup> conditions).

Alloisolongifolaldehyde (8) was prepared<sup>7</sup> by the  $\text{BF}_3 \cdot \text{OEt}_2$  isomerization of the epoxide resulting from peracid oxidation of alloisolongifolene (1). The diazoketone (16), obtained by the action of  $\text{CH}_2\text{N}_2$  on the acid chloride (15) from alloisolongifolic acid (14), on reduction<sup>8</sup> with 47% aq. hydriodic acid gave the methyl ketone (11). The required tosylhydrazones 9/12 were readily prepared by refluxing 8/11 with tosylhydrazine in chloroform (PMR: *syn/anti* mixture of isomers in both cases). The fate of the monoalkylcarbene 6 generated when 9 was refluxed with sodium methoxide in diglyme, was then studied.

†NCL Communication No. 447.

The resulting mixture was chromatographed over silica gel to afford the hydrocarbon part (light petroleum-eluted, ~40%), the  $\text{Ag}^+$ -silica gel TLC of which indicated two distinct spots and was therefore further resolved on a column of this adsorbent. The slower-moving major constituent (30%) was readily identified as 1 by direct comparison. More interesting, however, was the faster-moving minor compound (9%) which analysed for  $\text{C}_{15}\text{H}_{24}$  ( $M^+$  204, base peak) and gave a faint yellow colour with TNM and was clearly the cyclopropane derivative 17 on the basis of its spectral features. Thus, its PMR spectrum was characterized by a cluster of six high field singlets between  $\delta$  0.26-0.60 (5H) and two tertiary methyl singlets at  $\delta$  0.76 and 0.84 while the absence of olefinic protons was borne out by a transparent downfield region above  $\delta$  2.0; further more, strong bands at 3100, 1020, 825  $\text{cm}^{-1}$  characteristic<sup>9</sup> of cyclopropane were also present in its IR spectrum. Thus, in the case of 6 (in which one of the methyls is fully substituted by ring residues) also, products of both 1,2 and 1,3 carbon-hydrogen insertion are generated, again the former being the major pathway. From the remaining more polar chromatographic fractions however, no pure compound could be isolated. The protic Bamford-Stevens reaction (sodium in ethylene glycol) on 9 was characterized by formation of the 2-hydroxyethyl ether<sup>10</sup> (18) which could be readily separated by chromatography from the only hydrocarbon, 1 (54%) formed in the reaction.

In order to generate the dialkylcarbene (7), the tosylhydrazone (12) (from the methyl ketone 11) was subjected to the aprotic Bamford-Stevens reaction and the products isolated as before by a combination of



chromatography on silica gel/Ag<sup>+</sup>-silica gel. In this case also, insertion into the adjacent carbon-hydrogen bond was the major pathway generating the olefin (**19**) (42 %) while the 1,3-insertion product (**20**) was only in a trace amount (2 %). From the PMR spectrum of **20** (C<sub>16</sub>H<sub>26</sub>; M<sup>+</sup> 218, base peak) it was clearly a mixture of *cis*-**20a**/*trans*-**20b** isomers. When **12** was refluxed with the sodium salt of ethylene glycol in the same solvent, the major product was **19** (20 %); **20** and the 2-hydroxyethyl ether (**21**) (8 %) were also isolated and suitably characterized.

### Experimental Procedure

For general experimental instructions, see Part I of the series<sup>1</sup>.

#### Alloisolongifolaldehyde tosylhydrazone (**9**)

Alloisolongifolaldehyde (**8**, 6 g) and tosylhydrazine (6.1 g) in CHCl<sub>3</sub> (100 ml) were refluxed on a water-bath for 18 hr, concentrated to dryness and the residue recrystallized from MeOH to yield the **9** as white needles m.p. 110-13 °C (7.5 g, 72 %); IR (nujol): 3220, 1635, 1600, 1170, 1085, 820; PMR(CDCl<sub>3</sub>): δ 7.92 (d,

2H, aromatic,  $J = 8$  Hz), 7.36 (d, 2H, aromatic,  $J = 8$  Hz), 7.20 (d, 1H,  $-\dot{\text{C}}\text{H}-\text{CH}=\text{N}-\text{NH}-$ ,  $J = 6$  Hz), 2.52 (s, 3H, aromatic methyl), 0.94 (d, 3H, secondary methyl,  $J = 6$  Hz), 0.88, 0.84, 0.80, 0.72 (tertiary Me singlets; *syn/anti* isomeric mixture).

*Aprotic Bamford-Stevens reaction on 9: Formation of alloisolongifolene (1) and the cyclopropane derivative (17)*

**9** (2 g) was added to a solution of NaOMe (1.1 g) in diglyme (20 ml) and refluxed for 1 hr. The mixture was quenched in cold water (100 ml), extracted with light petroleum ( $3 \times 40$  ml), washed with brine, dried, solvent removed and the residue chromatographed on  $\text{SiO}_2$  gel (with TLC monitoring): Fr. 1, light petroleum, 75 ml, 425 mg, mixture ( $\text{AgNO}_3$ -TLC; 2 spots). Fr. 2, 50% benzene-light petroleum,  $2 \times 40$  ml, 173 mg, mixture.

Fr. 1 was chromatographed over 15%  $\text{AgNO}_3$ - $\text{SiO}_2$  gel (with TLC monitoring): Fr. 1a, light petroleum, 50 ml, pure **17**, colourless liquid b.p.  $90^\circ$  (bath)/0.6 mm (95 mg, 9%); IR(smear): 3100, 1020, 825; PMR( $\text{CDCl}_3$ ):  $\delta$  0.84, 0.76 (two tertiary Me singlets), 0.26-0.60 (cluster of six singlets, 5H, cyclopropanic; MS:  $m/z$  204 ( $\text{M}^+$ , base peak) (Found: C, 87.6; H, 12.2.  $\text{C}_{15}\text{H}_{24}$  requires C, 88.2; H, 11.8%). Fr. 1b, light petroleum,  $4 \times 30$  ml, pure **1** (319 mg, 30%), identified by IR/PMR.

*Protic Bamford-Stevens reaction on 9: Formation of 1 and 2-hydroxyethyl ether (18)*

**9** (3 g) was added to a solution of metallic sodium (0.7 g) in ethylene glycol (30 ml) and refluxed for 1 hr. The mixture was quenched in cold water, extracted with light petroleum ( $3 \times 60$  ml), washed with brine, dried, solvent removed and the residue chromatographed over  $\text{SiO}_2$  gel (with TLC monitoring): Fr. 1, light petroleum, 75 ml, pure **1** (878 mg, 54%), identified by IR/PMR. Fr. 2, 2% EtOAc-benzene,  $3 \times 40$  ml, pure.

Fr. 2 was distilled to give **18** (C-11 epimeric mixture) as thick colourless liquid, b.p.  $155^\circ$  (bath)/0.7 mm (505 mg, 24%); IR (smear): 3450, 1120, 1065; PMR ( $\text{CDCl}_3$ ):  $\delta$  3.30-3.68 (m, 6H,  $-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH}$ ), 0.72-0.96 (9H, one *sec* and two *tert* methyls); MS:  $m/z$  266 ( $\text{M}^+$ , base peak) (Found: C, 76.5; H, 11.4.  $\text{C}_{17}\text{H}_{30}\text{O}_2$  requires C, 76.6; H, 11.4%).

*Methyl ketone tosylhydrazone (12)*

A mixture of the acid (**14**, 8 g) and thionyl chloride (7 ml) was kept at room temperature for 18 hr (gas absorption trap). After removal of excess of  $\text{SOCl}_2$  the residue was distilled to yield the acid chloride (**15**) as a colourless liquid b.p.  $110^\circ$  (1 mm) (7.2 g, 88%).

A cold solution of **15** (7.2 g) in dry ether (25 ml) was added dropwise to a stirred ethereal solution of

diazomethane (5.4 of  $\text{CH}_2\text{N}_2$  in 200 ml of dry ether) cooled in an ice-bath. After addition (0.5 hr), the mixture was kept at room temperature for 18 hr. Removal of solvent gave the diazoketone (**16**, 8 g); IR (nujol): 2120, 1640. To crude **16** (8 g) in  $\text{CHCl}_3$  (115 ml) was added 47% aq. hydriodic acid (19 ml) while stirring at room temperature. After nitrogen evolution stopped, the mixture was diluted with water, the separated chloroform layer washed with water, aq.  $\text{Na}_2\text{S}_2\text{O}_3$ , brine, dried, solvent removed and the residue distilled to give **11** as a colourless liquid, b.p.  $110^\circ$ /1 mm (5.6 g, 78%); IR(smear): 1700; PMR( $\text{CDCl}_3$ ):  $\delta$  2.61 (q, 1H,  $-\text{CH}_3-\dot{\text{C}}\text{H}-\text{COCH}_3$ ,  $J = 6$  Hz), 2.00 (s, 3H,  $\text{CH}_3-\text{CO}-$ ), 0.94 (d, *sec*-Me,  $J = 7$  Hz); 0.87, 0.78 (two *tert*. Me singlets); MS:  $m/z$  234 ( $\text{M}^+$ ) (Found: C, 82.0; H, 11.3.  $\text{C}_{16}\text{H}_{26}\text{O}$  requires: C, 82.0; H, 11.2%).

The methyl ketone (**11**, 4.5 g) and tosylhydrazine (2.9 g) in  $\text{CHCl}_3$  (30 ml) were refluxed on a water-bath (18 hr) and the product recrystallized from MeOH to furnish colourless needles of **12**, m.p.  $145-47^\circ$  (d) (6 g, 78%); IR(nujol): 3250, 1640, 1600, 1175, 820; PMR( $\text{CCl}_4$ ):  $\delta$  7.77 (d, 2H, aromatic,  $J = 8$  Hz), 7.20 (d, 2H, aromatic,  $J = 8$  Hz), 2.55 (q, 1H,  $-\text{CH}_3-\dot{\text{C}}\text{H}-\text{C}=\text{N}-\text{NH}-$ ,  $J = 7$  Hz), 2.40 (s, 3H, aromatic methyl), 1.70 (s, 3H,  $\text{CH}_3-\dot{\text{C}}=\text{N}-\text{NH}-$ ), 0.88 (d, 3H, *sec* methyl,  $J = 7$  Hz); 0.78, 0.73  $\times$  2, 0.65 (tertiary Me singlets of *syn/anti* isomers) (Found: C, 68.7; H, 8.7; N, 7.4; S, 7.9.  $\text{C}_{23}\text{H}_{34}\text{O}_2\text{N}_2\text{S}$  requires C, 68.6; H, 8.5; N, 7.0; S, 8.0%).

*Aprotic Bamford-Stevens reaction on 12: Formation of olefin (19) and 1,3-insertion product (20)*

**12** (2 g) was refluxed (1 hr) in diglyme (25 ml) with NaOMe (1.1 g). The mixture was worked-up as usual and the crude product chromatographed on  $\text{SiO}_2$  gel. Fr. 1, light petroleum,  $2 \times 50$  ml, 496 mg, mixture ( $\text{AgNO}_3$ -TLC; 2 spots). Fr. 2, 10% EtOAc-benzene,  $2 \times 30$  ml, 200 mg, mixture.

Fr. 1 was chromatographed over 15%  $\text{AgNO}_3$ - $\text{SiO}_2$  as before. Fr. 1a, light petroleum, 20 ml, pure 1,3-insertion product (**20**), colourless liquid, b.p.  $100^\circ$  (bath)/1.5 mm (25 mg, 2%); IR (smear): 3100, 810; PMR ( $\text{CDCl}_3$ ):  $\delta$  1.05, 1.02 (*sec*. Me doublets of **20a** **20b**,  $J = 6$  Hz), 0.83, 0.76 (tertiary Me singlets of **20a** **20b**), 0.20-0.62 (m, 4H, cyclopropanic); MS:  $m/z$  218 ( $\text{M}^+$ , base peak) (Found: C, 88.1; H, 12.3.  $\text{C}_{16}\text{H}_{26}$  requires: C, 88.0; H, 12.0%). Fr. 1b, light petroleum,  $4 \times 30$  ml, pure **19**, colourless liquid  $105^\circ$  (bath)/1.5 mm (287 mg, 20%); IR(smear): 1670, 830, PMR ( $\text{CDCl}_3$ ):  $\delta$  5.22 (q further split by allylic coupling, 1H,  $\text{CH}_3-\text{CH}=\dot{\text{C}}-\text{CH}_3$ ,  $J_1 = 7$  Hz,  $J_2 = 2$  Hz), 1.58 (d, 3H,  $\text{CH}_3-\text{CH}=\dot{\text{C}}-$ ,  $J = 7$  Hz), 1.54 (s, 3H,  $=\dot{\text{C}}-\text{CH}_3$ ), 0.88, 0.77 (two tertiary Me singlets); MS:  $m/z$  218 ( $\text{M}^+$ , base peak) (Found: C, 87.7; H, 12.0.  $\text{C}_{16}\text{H}_{26}$  requires C, 88.0; H, 12.0%).

*Protic Bamford-Stevens reaction on 12:**Formation of 19, 20 and 2-hydroxyethyl ether (21)*

12 (2.6 g) was added to a solution of metallic sodium (0.6 g) in ethylene glycol (30 ml) and refluxed for 1 hr. The mixture was worked-up as described for 9 and the residue chromatographed on SiO<sub>2</sub>. Fr. 1, light petroleum, 2 × 60 ml, mixture (376 mg, AgNO<sub>3</sub>-TLC; 2 spots). Fr. 2, 25% benzene-light petroleum, 3 × 40 ml, 133 mg, mixture. Fr. 3, 2% EtOAc-benzene, 3 × 30 ml, pure.

Fr. 3 was distilled to give 21 (C-12 epimeric mixture) as thick colourless liquid, b.p. 165° (bath)/2 mm (148 mg, 8%); IR(smear): 3460, 1125, 1075; PMR(CCl<sub>4</sub>): δ 3.10-3.60 (m, 5H, CH<sub>3</sub>-CH-O-CH<sub>2</sub>-CH<sub>2</sub>-OH), 1.12 (d, CH<sub>3</sub>-CH-O-, J=7 Hz), 1.05 (d, CH<sub>3</sub>-CH-, J=7 Hz); 0.80 to 0.90 (9H, one *sec* Me and two *tert.* Me singlets); MS: *m/z* 280 (M<sup>+</sup>).

Fr. 1 was chromatographed over AgNO<sub>3</sub>-SiO<sub>2</sub> gel as before. Fr. 1a, light petroleum (30 ml), cyclopropane derivative 20 (69 mg, 5%), identified by IR/PMR. Fr. 1b, light petroleum (4 × 30 ml), pure 19 (287 mg, 20%), identified by IR/PMR.

**References**

- 1 Satyanarayana N & Nayak U R, *Indian J Chem*, **25B** (1986) 22.
- 2 Satyanarayana N & Nayak U R, *Indian J Chem*, **25B** (1986) 28.
- 3 (a) Shitole H R, Vyas P & Nayak U R, *Tetrahedron Lett*, **24** (1983) 2411.  
(b) Shitole H R, Dalavoy V S, Deodhar V B, Nayak U R, Acharya K R, Tavale S S, Guru Row T N, Kamat V P & Paknikar S K, *Tetrahedron Lett*, **24** (1983) 4739.  
(c) Shitole H R, Vyas P & Nayak U R, *Indian J Chem*, **23B** (1984) 702.
- 4 (a) Kirmse W, *Carbene chemistry* (Academic Press, New York) 1971, pp. 29-34.  
(b) Brown W J, Decamp M R, Hendrick M E, Jones M (Jr), Levin R H & Sohn M B, *Carbenes*, Vol. 1 edited by Jones M (Jr) & R A Moss (Wiley-Interscience, New York), 1973, pp. 1-151.
- 5 Friedman L & Schechter H, *J Am chem Soc*, **81** (1959) 5512.
- 6 (a) Bamford W R & Stevens T S, *J chem Soc*, (1952) 4735.  
(b) Shapiro R H, *Organic Reactions*, **23** (1976) 405.  
(c) Casanova J & Waegell B, *Bull Soc chim Fr*, (1975) 922.
- 7 Shitole H R & Nayak U R, *Indian J Chem*, **23B** (1984) 707.
- 8 (a) Wolfrom M L & Brown R L, *J Am chem Soc*, **65** (1943) 1516.  
(b) Wolfrom M L & Bennett R B, *J org Chem*, **30** (1965) 458.  
(c) Satyanarayana N, Shitole H R & Nayak U R, *Indian J Chem*, **24B** (1985) 997.
- 9 Bellamy L J, *The infrared spectra of complex molecules*, Vol. 2 (Chapman & Hall, London) 1980, pp. 12 and 21.
- 10 Paquette L A & Birnberg G H, *J Am chem Soc*, **94** (1972) 164.

# Longihomocamphenilane-7,8-dione: Reactivity of Carbonyl Groups via Monofunctional Derivatives of the Diketone†

S P VAIDYA, H R SHITOLE & U R NAYAK\*

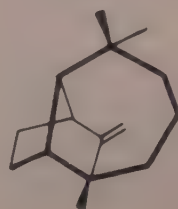
National Chemical Laboratory, Poona 411 008

Received 10 June 1985; accepted 26 June 1985

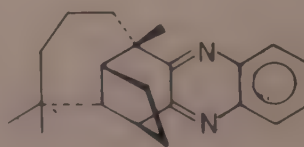
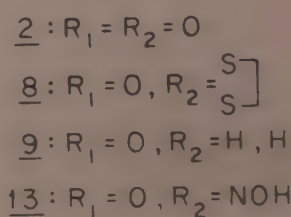
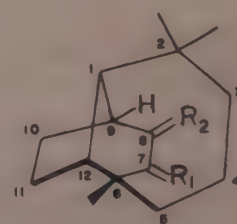
Formation of the C-7 ketone, longiisohomocamphenilone (9), by Raney Nickel desulphurization of the monothioketal of longihomocamphenilane-7,8-dione (2), fixes C-8 as the reactive carbonyl (attached to a secondary carbon) of the diketone; longicamphorquinone (4), however, gives longiepicamphor (6) instead of the expected longicamphor (7) by this method. The monoxime derived from 2, on exposure to tosyl chloride/aq KOH, undergoes a Beckmann fragmentation to give the cyano acid (14) which also fixes C-8 carbonyl as the reactive of the two in 2. Kochi oxidative decarboxylation of 14 with Pb(IV)-Cu(II) gives the vinylidene nitrile (17) as the major product.

Longihomocamphenilane-7,8-dione (2) (hereafter abbreviated as longidione) is a ring-enlarged bridged, tricyclic  $\alpha$ -diketone derived<sup>1</sup> from longifolene (1) by reaction with a variety of oxidants but generally formed in poor yields. It has been characterized<sup>2</sup> by the preparation of its monosemicarbazone, monophenylhydrazone, mono-*p*-bromophenylhydrazone and monoxime. Apart from the quinoxaline derivative (3) (formed by reaction with *o*-phenylenediamine), no derivative in which the second carbonyl group has reacted<sup>2</sup> has been prepared. It has also been proved<sup>3</sup> that longidione possesses alpha to the dicarbonyl group only a single unenolizable hydrogen atom presumably at the bridgehead as in 2. Since 2 is known to yield only homogeneous mono derivatives, the carbonyl at C-7 was presumed<sup>2</sup> to be the more hindered since it was attached to a tertiary carbon as compared to C-8 carbonyl which was attached to secondary carbon. Since we have experimental proof (*vide infra*) that this statement is not generally true, it became necessary to provide chemical evidence which unambiguously fixes the C-8 carbonyl as the reactive moiety of 2.

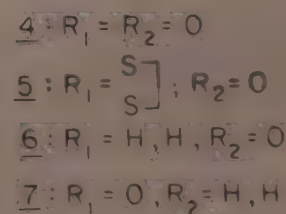
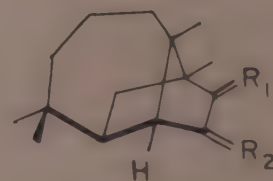
Longicamphorquinone<sup>4</sup> (4), a 1,2-diketone structurally closely related to 2, on treatment with ethanedithiol/boron trifluoride etherate, afforded only a monothioketal (5) which on Raney nickel desulphurization gave instead of longicamphor<sup>5</sup> (7) the isomer longiepicamphor (6). 7 would have been formed had ethanedithiol attacked the carbonyl attached to the secondary carbon in 4. When the monothioketal of 2 was similarly prepared and desulphurized, the resulting monoketone was identified with the known C-7 ketone, longiisohomocamphenilone (9), on this basis its precursor thioketal should be formulated as 8.



1



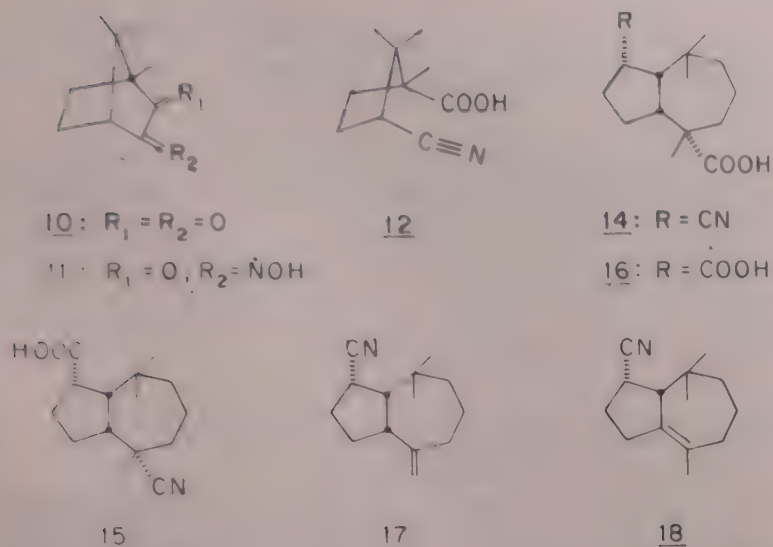
3



In the latter case thioketal formation occurred at the carbonyl attached to the secondary carbon while in the case of 4 the carbonyl linked to the tertiary carbon was involved in thioketal formation.

In an earlier paper<sup>7</sup> we have described the tosyl chloride pyridine-induced Beckmann fragmentation<sup>8</sup> of the ketoximes derived from the pair camphor [longicamphor]. In the present work, the monoxime (11) of camphorquinone (10) was also treated with tosyl chloride but in aqueous alkali at ambient temperature. The crystalline product, isolated from the alkaline

\*NCL Communication No. 1845



reaction mixture by acidification, was readily characterized as the cyano acid (12), arising from a Beckmann fission. Under similar reaction conditions, the monoxime of 2 also gave a cyano acid (m.p. 129°; 53%) for which structure 14 (and not 15) could be assigned on the basis of its PMR data: the downfield 3H-singlet at  $\delta$  1.37 is characteristic<sup>10</sup> of the tertiary methyl on a carbon bearing a carboxyl group. Such a situation is obtainable in 14 only; this fixes the oxime structure as 13. The cyano group in 14 was however quite resistant to hydrolysis; even after refluxing the compound in ethylene glycolic KOH for several hours, it failed to give  $\alpha$ -longiforic acid<sup>9</sup> (16). In conformity with the assigned structure (14), the cyano acid gave the vinylidene nitrile (17) (plus minor amount of 18) on Kochi<sup>11</sup> oxidative decarboxylation with Pb(IV)-Cu(II); this chemical evidence also confirms structure (13) for its progenitor oxime.

### Experimental Procedure

All m.ps and b.ps are uncorrected. Light petroleum refers to the fraction b.p. 60–80°. Solvent extracts were dried over anhydrous  $Na_2SO_4$ . Tosyl chloride used was freshly purified<sup>12</sup> and recrystallized. IR spectra ( $\nu_{max}$  in  $cm^{-1}$ ) were recorded as smears (liquid) or nujol mulls (solid) on a Pye-Unicam SP-3 IR spectrophotometer, PMR spectra on a Varian T 60/FT 80A/Bruker WH-90 FT spectrometers and mass spectra (MS) on a CEC spectrometer model 21-110B, using an ionizing voltage of 70 eV and a direct inlet system.

Longidione (2) was prepared from  $\omega$ -bromolongifolene via the simplified sequence of reactions described by Desphande *et al.*<sup>9</sup>.

### Longidione quinoxaline (3)

A mixture of 2 (2.34 g), AcOH (25 ml) and *o*-phenylenediamine (2.34 g) was refluxed for 4 hr. The mixture was quenched in ice water, the separated solid was filtered off and recrystallized from MeOH to give

colourless crystals of 3, m.p. 134° (2 g, 66%); IR (nujol): 1550, 772; PMR ( $CCl_4$ ):  $\delta$  7.40 to 8.00 (*m*, 4H, aromatic), 3.43 (*m*, 1H, HC–C=N as in 3), 1.37, 1.10, 0.93 (three tertiary Me singlets); MS:  $m/z$  306 ( $M^+$ , base peak) (Found: C, 82.6; H, 8.6; N, 8.8.  $C_{21}H_{26}N_2$  requires C, 82.3; H, 8.6; N, 9.1%).

### Longicamphorquinone (4)

This was prepared by the action of  $SeO_2$ -AcOH on longicamphor.

### Longicamphorquinone monothioacetal (5)

A mixture of 4 (1.2 g), AcOH (1 ml), ethanedithiol (0.6 mol) and  $BF_3 \cdot OEt_2$  (0.6 ml) was kept at room temperature, overnight. The separated solid was filtered off and recrystallized from MeOH to give 5 as colourless needles, m.p. 142–44° (0.85 g, 52%); IR (nujol): 1740, 1180, 1100, 865; PMR ( $CCl_4$ ):  $\delta$  2.93 to 3.57 (*m*, 4H,  $2 \times CH_2$ , thioketal methylenes), 1.12, 1.02  $\times 2$ , 0.82 (four tertiary Me singlets) (Found: C, 65.1; H, 8.6; S, 20.0.  $C_{17}H_{26}OS_2$  requires C, 65.8; H, 8.4; S, 20.6%).

### Desulphurization of 5: Formation of longiepicaamphor (6)

A mixture of 5 (0.5 g), ethanol (50 ml) and Raney nickel (W-2, 5 g) was refluxed on a water-bath (17 hr), filtered, the precipitate thoroughly washed with more EtOH and the filtrate taken to dryness. Distillation of the residue gave 6 as a colourless liquid b.p. 125° (bath)/0.5 mm which solidified, m.p. 55° (0.25 g; 69%); IR (nujol): 1740, 1420, 1200, 1170, 1060; PMR ( $CCl_4$ ):  $\delta$  1.05  $\times 2$ , 0.90, 0.83 (four tertiary Me singlets) (Found: C, 81.8; H, 11.4.  $C_{15}H_{24}O$  requires C, 81.8; H, 11.0%).

### Longidione monothioacetal (8)

A mixture of 2 (11.7 g), AcOH (10 ml), ethanedithiol (5 ml) and  $BF_3 \cdot OEt_2$  (5 ml) was kept at room temperature for 48 hr. The mixture was poured into water (50 ml), extracted with benzene ( $3 \times 100$  ml), the organic extract washed with aq  $NaHCO_3$ , brine, dried, solvent removed and the residue recrystallized from MeOH to afford 8 as colourless micro prisms, m.p. 99°–101° (4.2 g, 27%); IR (nujol): 1695, 1080, 990, 930; PMR ( $CCl_4$ ):  $\delta$  2.67 to 3.57 (*m*, 4H,  $2 \times CH_2$ , thioketal methylene), 1.20, 1.13, 1.02 (three tertiary Me singlets); MS:  $m/z$  310 ( $M^+$ , base peak) (Found: C, 65.9; H, 8.6; S, 19.7.  $C_{17}H_{26}OS_2$  requires C, 65.8; H, 8.4; S, 20.6%).

### Desulphurization of 8: Formation of longiisohomocamphenilone (9)

A mixture of 8 (1 g), ethanol (100 ml) and Raney nickel (W-2, 12 g) was refluxed (17 hr) and the isolated product, m.p. 68–69° (0.63 g, 69%) was identified as the C-7 ketone 9 (m.m.p. IR/PMR).

### Camphorquinone monoxime (11)

A mixture of camphorquinone (10, 5 g), ethanol (50 ml), hydroxylamine hydrochloride (2.3 g) and pyridine (2.3 ml) was refluxed for 1 hr. The mixture was diluted with water (200 ml), saturated with sodium chloride, extracted with benzene (100 ml  $\times$  3), organic extract washed with brine, dried, solvent removed and the residue recrystallized from benzene-light petroleum to give colourless prisms of 11, m.p. 112–14° (2.1 g, 38 %); IR (nujol): 3200, 1740, 1640, 1010, 940, 890; PMR (pyridine):  $\delta$  3.43 (d, 1H,  $-\text{CH}-\text{C}=\text{N}$  as in 11,  $J=4$  Hz), 1.03, 0.87  $\times$  2 (three tertiary methyl singlets); MS:  $m/z$  181 ( $\text{M}^+$ ) (Found: C, 65.6; H, 8.5; N, 8.8.  $\text{C}_{11}\text{H}_{15}\text{O}_2\text{N}$  requires C, 66.1; H, 8.3; N, 7.9 %).

### Action of tosyl chloride/aq. KOH on 11: Formation of cyano acid (12)

A solution of 11 (1.8 g) in aq KOH (3 g in 30 ml of water) was treated with tosyl chloride (1.9 g) and stirred for 3 hr. The mixture was diluted with water (50 ml), filtered and the filtrate acidified with HCl and cooled. The separated solid was filtered off and recrystallized from benzene to afford 12, m.p. 151–52° (0.95 g, 52 %); IR (nujol): 2200, 1690, 1290, 1170, 1130, 955; PMR ( $\text{CDCl}_3$ ):  $\delta$  11.09 (bs, 1H,  $-\text{COOH}$ ), 1.27, 1.25, 1.17 (three tertiary Me singlets) (Found: C, 66.6; H, 8.4; N, 7.3.  $\text{C}_{10}\text{H}_{15}\text{O}_2\text{N}$  requires C, 66.3; H, 8.3; N, 7.7 %).

### Longidione monoxime (13)

A mixture of 2 (14 g), ethanol (100 ml), hydroxylamine hydrochloride (5 g) and pyridine (5 ml) was refluxed on a water-bath (16 hr). The mixture was poured into water (200 ml), cooled, the separated solid filtered off and recrystallized from light petroleum to give colourless crystals of 13, m.p. 224–25° (11.3 g, 77 %); IR (nujol): 3000, 1700, 1600, 1060, 970, 940; PMR ( $\text{CDCl}_3$ ):  $\delta$  9.97 (b, 1H, NH, exchanges with  $\text{D}_2\text{O}$ ), 3.90 (m, 1H,  $\text{HC}-\overset{\text{I}}{\text{C}}=\text{N}$  as in 13), 1.13, 1.10, 1.02 (three tertiary Me singlets); MS:  $m/z$  249 ( $\text{M}^+$ ) (Found: C, 70.9; H, 9.6; N, 5.9.  $\text{C}_{15}\text{H}_{23}\text{O}_2\text{N}$  requires C, 72.3; H, 9.3; N, 5.6 %).

### Action of tosylchloride/aq KOH on 13: Formation of cyano acid (14)

A solution of 13 (20 g) in aq KOH (24 g in 240 ml) of water) was stirred and treated with tosyl chloride (16 g) in small portions (during 0.5 hr). After stirring for 1 hr more, the mixture was diluted with water (100 ml), filtered, the filtrate cooled acidified with HCl. The separated solid was filtered off and recrystallized from benzene-light petroleum to furnish colourless crystals of 14, m.p. 12–29° (10.5 g, 53 %); IR (nujol): 2500–2700 (br), 2100, 1680, 1260, 1190, 950; PMR ( $\text{CCl}_4$ ):  $\delta$  11.40 (bs, 1H,  $\text{COOH}$ ), 2.90 (m, 1H,  $-\text{HC}-\text{CH}=\text{CN}$  as in

14), 1.37, 1.18  $\times$  2 (three tertiary Me singlets) (Found: C, 72.3; H, 9.5; N, 5.6.  $\text{C}_{15}\text{H}_{23}\text{O}_2\text{N}$  requires C, 72.3; H, 9.3; N, 6.6 %).

Methyl ester of 14 ( $\text{CH}_2\text{N}_2$  method) was obtained as a colourless liquid, b.p. 200° (bath)/2 mm; IR (smear): 2200, 1725, 1240, 990; PMR ( $\text{CCl}_4$ ):  $\delta$  3.60 (s,  $\text{COOMe}$ ), 1.23, 1.10, 1.05 (three tertiary Me singlets); MS:  $m/z$  263 ( $\text{M}^+$ ) (Found: C, 73.5; H, 9.7; N, 5.3.  $\text{C}_{16}\text{H}_{25}\text{O}_2\text{N}$  requires C, 73.0; H, 9.6; N, 5.3 %).

### Pb(IV)-Cu(II) oxidative decarboxylation of 14: Formation of cyano olefins (17/18)

A mixture of 14 (15.1 g), dry benzene (600 ml), lead tetraacetate (61 g), pyridine (1 ml) and cupric acetate (1 g) was stirred under reflux for 2 hr. Excess LTA was decomposed by the addition of ethanediol (17 ml) with stirring (10 min). The mixture was cooled, benzene layer decanted off and the residue thoroughly extracted with more benzene (3  $\times$  100 ml). The combined organic extract was successively washed with 5 % aq KOH, water brine, dried, solvent removed and the residue distilled to yield a mixture of olefinic nitriles, b.p. 130–35°/1 mm (9.4 g). This was chromatographed on a column of 15 %  $\text{AgNO}_3$ -silica gel (250 g; 10 cm  $\times$  2.6 cm): Fr. 1, liquid petroleum-benzene (1:1), 6  $\times$  200 ml, pure. Fr. 2, benzene, 9  $\times$  200 ml, pure.

Fr. 1 was distilled to give the endocyclic olefin (18) as a colourless liquid, b.p. 160° (bath)/0.7 mm (1.35 g, 11 %); IR (smear): 2180, PMR ( $\text{CCl}_4$ ):  $\delta$  1.77 (bs, 3H, vinylic Me), 1.23, 1.17 (two tertiary Me singlets); PMR ( $\text{CDCl}_3$ : off-resonance): 134.26 (s,  $\text{C}=\text{N}$ ); 130.11 and 123.81 (two s,  $>\text{C}=\text{C}<$ ); MS:  $m/z$  203 (Found: C, 82.8; H, 10.1; N, 6.8.  $\text{C}_{14}\text{H}_{21}\text{N}$  requires C, 82.7; H, 10.4; N, 6.9 %).

Fr. 2 was distilled to furnish the vinylidene nitrile (17) as a colourless liquid, b.p. 170° (bath)/1 mm (5.1 g, 41 %), which became a waxy solid on keeping; m.p. 47–48°; IR (smear): 2900, 2180, 1625, 900; PMR ( $\text{CCl}_4$ ):  $\delta$  4.73 (s, 2H,  $>\text{C}=\text{CH}_2$ ), 1.13, 1.07 (two tertiary Me singlets); MS:  $m/z$  203 ( $\text{M}^+$ ) (Found: C, 82.1; H, 10.3; N, 7.5.  $\text{C}_{14}\text{H}_{21}\text{N}$  requires C, 82.7; H, 10.4; N, 6.9 %).

### References

- 1 For e.g. See a) Lhomme J & Ourisson G, *Recherches*, **15** (1966) 16.  
b) Jadhav P K & Nayak U R, *J scient ind Res*, **39** (1980) 36.  
c) Sukh Dev, *Prog Chem Org Nat Prod*, **40** (1981) 50.
- 2 Simonsen J L & Barton D H R, *The terpenes* Vol III, (Cambridge University Press) 1951, pp 96.
- 3 Naffa P & Ourisson G, *Bull Soc Chim Fr*, (1954) 115.
- 4 Shitole H R & Nayak U R, *Indian J Chem*, **23B** (1984) 415.
- 5 Suryawanshi S N & Nayak U R, *Tetrahedron Lett*, (1977) 2619, *Indian J Chem*, **19B** (1980) 1.
- 6 Mehra M M, Ghatge B B & Bhattacharyya S C, *Tetrahedron* **21** (1965) 811.
- 7 Sanyalrayana N, Shitole H R & Nayak U R, *Indian J Chem*, (in press) **24B** (1985) 997.

- 8 a) Donaruma L G & Heldt W Z, *Organic Reactions*, **11** (1960) 1.
- b) Smith P A S in *Molecular rearrangements* Vol I edited by P de Mayo (Interscience, New York) 1963, pp 483.
- c) Conley R T & Ghosh S in, *Mechanisms of molecular migrations*, Vol 4, edited by B S Thyagarajan (Wiley, New York) 1971, pp 197.
- 9 Deshpande R P, Suryawanshi S N & Nayak U R, *Indian J Chem*, **17B** (1979) 617.
- 10 Gokhale P D, Joshi A P, Sahni R, Naik V G, Damodaran N P, Nayak U R & Sukh Dev, *Tetrahedron*, **32** (1976) 1391.
- 11 Sheldon R A & Kochi J K, *Organic Reactions*, **19** (1972) 279.
- 12 Fieser L F & Fieser M, *Reagents for organic synthesis*, Vol I (John Wiley, New York) 1967, pp 1179.

# 9-Methylenelongibornane†: Lewis Acid-induced Transannular Hydride Shift/Rearrangement to 9-Methylisolongifolene/7-Isopropyl-1,1,3-trimethyltetralin‡

S P VAIDYA & U R NAYAK\*

National Chemical Laboratory, Pune 411 008

Received 27 May 1985; accepted 8 July 1985

9-Methylisolongibornyl-9-cation (**5**, R = Me) generated from 9-methylenelongibornane (**2**), on exposure to  $\text{BF}_3\text{OEt}_2$  in benzene, has been shown to undergo a transannular 1,5-hydride shift in the "reverse" fashion (C-2 to C-9) to give the crucial 9-methylisolongibornyl-2-cation (**6**, R = Me) which then traverses the familiar Berson mechanistic pathway [entirely analogous to that of longifolene (**1**) → isolongifolene (**13**, R = H)] ending up finally in 9-methylisolongifolene (**13**, R = Me). Furthermore, 1,1,3-trimethyl-7-isopropyltetralin (**17**, R = Me) has also been isolated from **2** [via **13** (R = Me)] in a second-stage rearrangement under more energetic conditions, reminiscent of the transformation of isolongifolene (**13**, R = H) → 1,1-dimethyl-7-isopropyltetralin (**17**, R = H). The tetralin (**17**, R = Me) has also been synthesized from cumene in eight steps.

The synthesis of 9-methylenelongibornane (**2**) and some of its reactions have been described<sup>1</sup> recently. Longifolene (**1**) and **2** both incorporate an exocyclic methylene moiety in their structures but they differ in one important respect: whereas **1** can, of necessity, only undergo transannular reactions<sup>2</sup> and deep-seated rearrangements<sup>2</sup> independent of each other, theoretically **2** can successively suffer both of these. The carbocation **5** derived from **2** is spatially so placed (see **2a**) that it can initiate a transannular 1,5-hydride shift in the "reverse" fashion<sup>3</sup>, i.e. from C-2 to C-9. The crucial longibornyl-2-cation (**6**, R = Me) thus generated is now well-set for the familiar deep-seated multiple rearrangements following the Berson<sup>4</sup> mechanistic pathway to finally collapse into the isolongifolene skeleton (**13**, R = Me) (Scheme 1). Practical realization of this theoretical rationale forms the highlight of this paper.

The Lewis acid,  $\text{BF}_3\text{OEt}_2$ , has proved to be extremely useful for the transformation<sup>5</sup> of **1** into isolongifolene (**13**, R = H) under mild conditions. (catalytic amount in benzene at ambient temperature). When these conditions were applied to **2**, however, the double bond just migrated inside the ring generating<sup>1</sup>

the endocyclic olefin **3** and no other deep-seated change was noted.

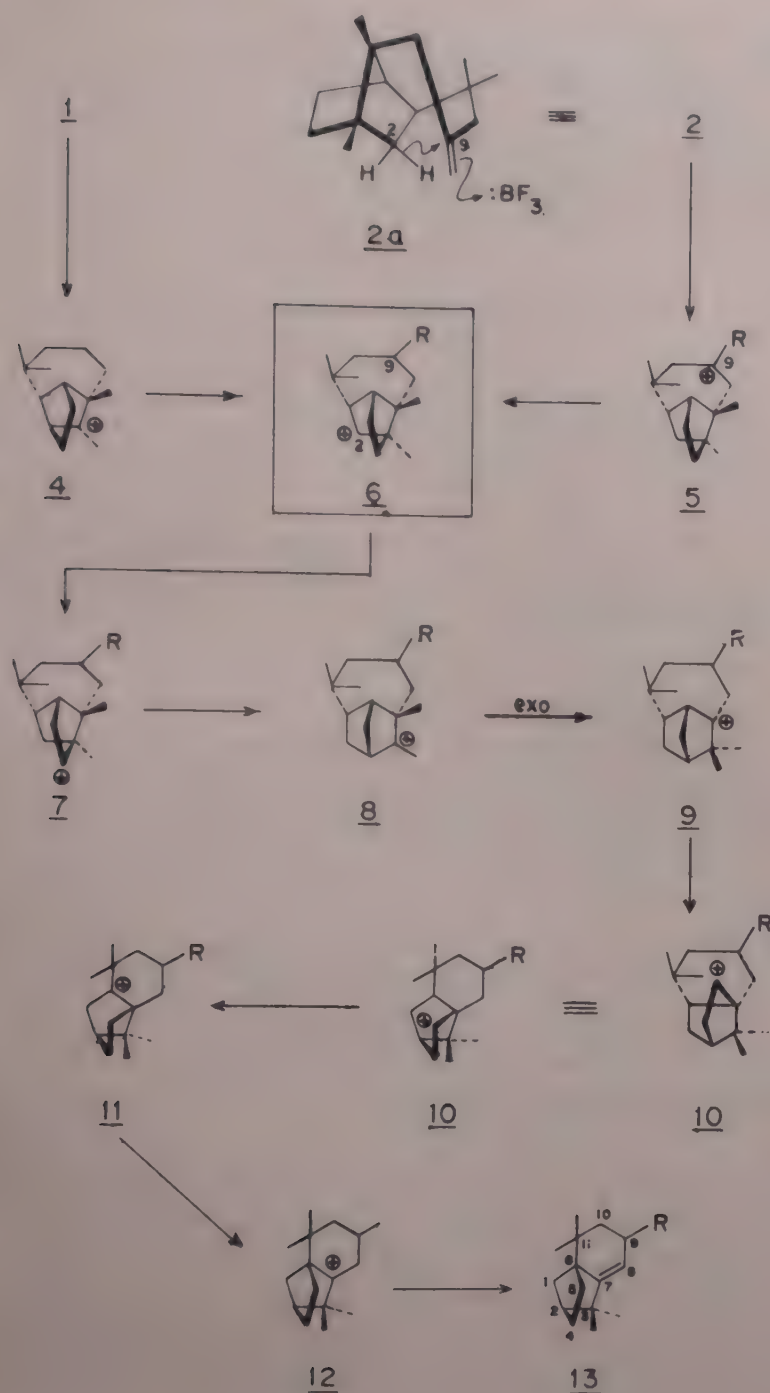
Refluxing the reaction mixture for a prolonged period failed to bring about any further transformation of **3**. Only when the amount of the Lewis acid was increased tenfold (in refluxing benzene) was there an indication of the formation of a new compound ( $\text{AgNO}_3$ -silica gel TLC: 2 spots) which was then separated from **3** (13%) by chromatography over this adsorbent. The faster-moving new hydrocarbon,  $\text{C}_{16}\text{H}_{26}$  ( $M^+$  218) (16%) was readily characterized as the sought-after (see Scheme 1) 9-methylisolongifolene (**13**, R = Me) by the multiplicity of the lone olefinic proton in its PMR spectrum, which was quite diagnostic; while in the case of isolongifolene (**13**, R = H) it appeared as a triplet, in 9-methyl derivative (**13**, R = Me) it appeared as a doublet at  $\delta$  4.95 ( $J$  = 2 Hz) which is in accord with a single neighbouring proton (of the secondary methyl at C-9).

Further rearrangement<sup>6</sup>/disproportionation<sup>6</sup> of **13** (R = Me) (Scheme 2) could also be achieved when 9-methylenelongibornane (**2**) was exposed to  $\text{BF}_3\text{OEt}_2$  at a higher temperature (refluxing toluene). On chromatography of the resulting mixture on a column of 15%  $\text{AgNO}_3$ -silica gel, two pure hydrocarbons were separated and characterized as the tetralin (**17**, R = Me; 18%) and the octalin (**18**, R = Me; 20%) on the basis of their spectral features.

The structure of **17** (R = Me), which is new, has also been confirmed by direct comparison with an authentic specimen prepared from isopropylbenzene via the succinic anhydride route<sup>7</sup>. Since methylsuccinic anhydride would give the wrong positional isomer of **17** (R = Me), i.e. 1,1,2-trimethyl-7-isopropyltetralin (the



\*Part 2. For Part 1 see Goudgaon V M, Shitole H R & Nayak U R, Indian J Chem, 24B (1986) 350.  
†NCL Communication No. 8836



SCHEME 1

### Experimental Procedure

All m.p's and b.p's are uncorrected. Light petroleum refers to the fraction b.p. 60-80°. Freshly purified<sup>10</sup> and distilled borontrifluoride etherate was used.  $\text{AgNO}_3$ -silica gel was prepared by the method of Gupta and Dev<sup>11</sup>.  $\text{BF}_3 \cdot \text{OEt}_2$ -rearrangement reactions of 2 and chromatographic separations were monitored by TLC on  $\text{AgNO}_3$ -silica gel. Solvent extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ . IR spectra ( $\nu_{\text{max}}$  in  $\text{cm}^{-1}$ ) were recorded as smears (liquid) or nujol mulls (solid) on Pye-Unicam SP-3 IR spectrophotometer, PMR spectra on Varian T60/FT 80A/Bruker WH-90 spectrometers and mass spectra (MS) on a CEC spectrometer model H-110B, using an ionizing voltage of 70 eV and a direct inlet system.

9-Methylenelongibornane (2) was prepared<sup>1</sup> by the Wittig reaction on longibornane-9-one using  $\text{Ph}_3\text{P}=\text{CH}_2$ .

*Action of  $\text{BF}_3 \cdot \text{OEt}_2$  on 2 (refluxing benzene):*

*Formation of olefin 3/9-methylisolongifolene (13, R = Me)*

A mixture containing 2 (3 g), dry benzene (50 ml) and  $\text{BF}_3 \cdot \text{OEt}_2$  (0.1 ml) was refluxed on a water-bath (17 hr). The mixture was diluted with more benzene, washed with aq.  $\text{NaHCO}_3$ , brine, dried, solvent removed and the residue distilled to give pure 3 (IR/PMR).

A mixture of 2 (1 g), benzene (20 ml) and  $\text{BF}_3 \cdot \text{OEt}_2$  (0.3 ml) was refluxed and worked-up as before and the product was chromatographed on a column of 15%  $\text{AgNO}_3$ -silica gel: Fr. 1, light petroleum, 4 × 25 ml, pure 13 (R = Me), colourless liquid, b.p. 110° (bath)/0.5 mm (0.155 g, 16%); IR(smear): 1390, 1370, 860, 840; PMR( $\text{CDCl}_3$ ):  $\delta$  4.96 (d, 1H,  $-\text{C}=\text{CH}-\text{CH}-\text{Me}$ ,  $J=2$  Hz), 0.90 (d, 3H, s-Me,  $J=8$  Hz); 1.02, 0.95, 0.91, 0.84 (four tertiary Me singlets); MS:  $m/z$  218 ( $\text{M}^+$ ) (Found: C, 88.8; H, 11.6.  $\text{C}_{16}\text{H}_{26}$  requires C, 88.1; H, 11.9%).

Fr. 2, light petroleum, 2 × 25 ml, olefin 3 (13%) (IR/PMR).

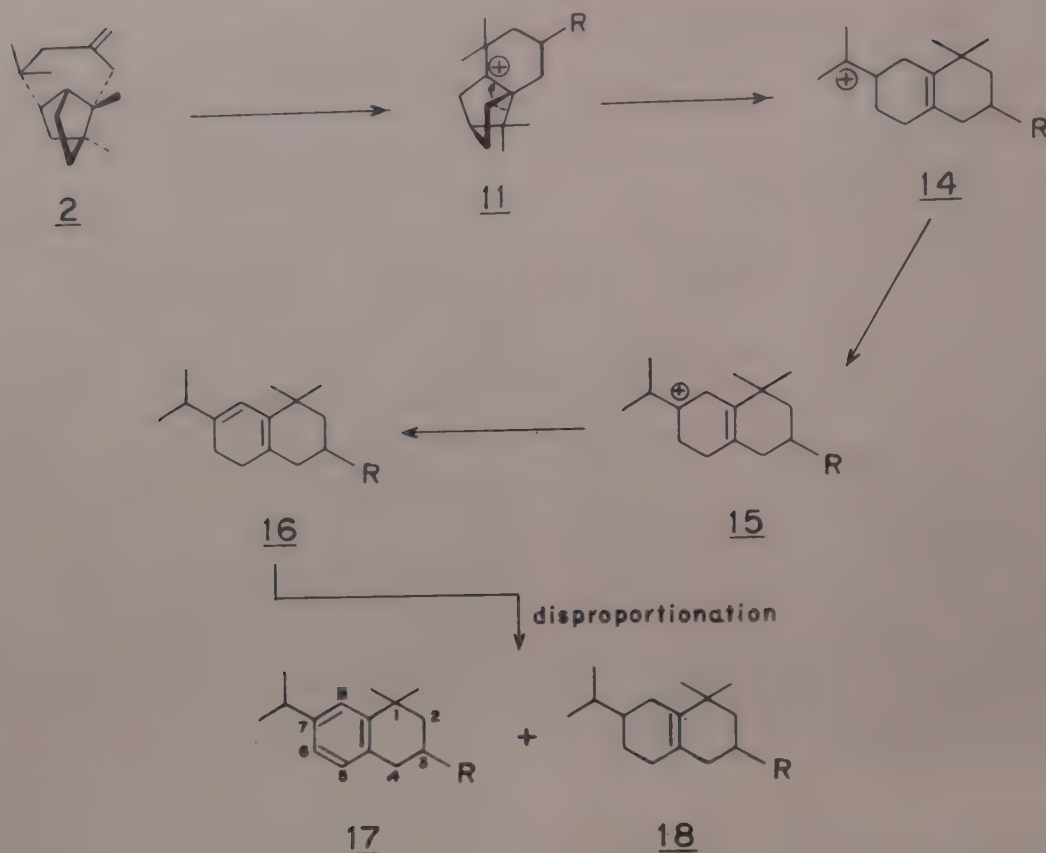
*Action of  $\text{BF}_3 \cdot \text{OEt}_2$  on 2 (refluxing toluene):*

*Formation of tetralin (17, R = Me)/octalin (18, R = Me)*

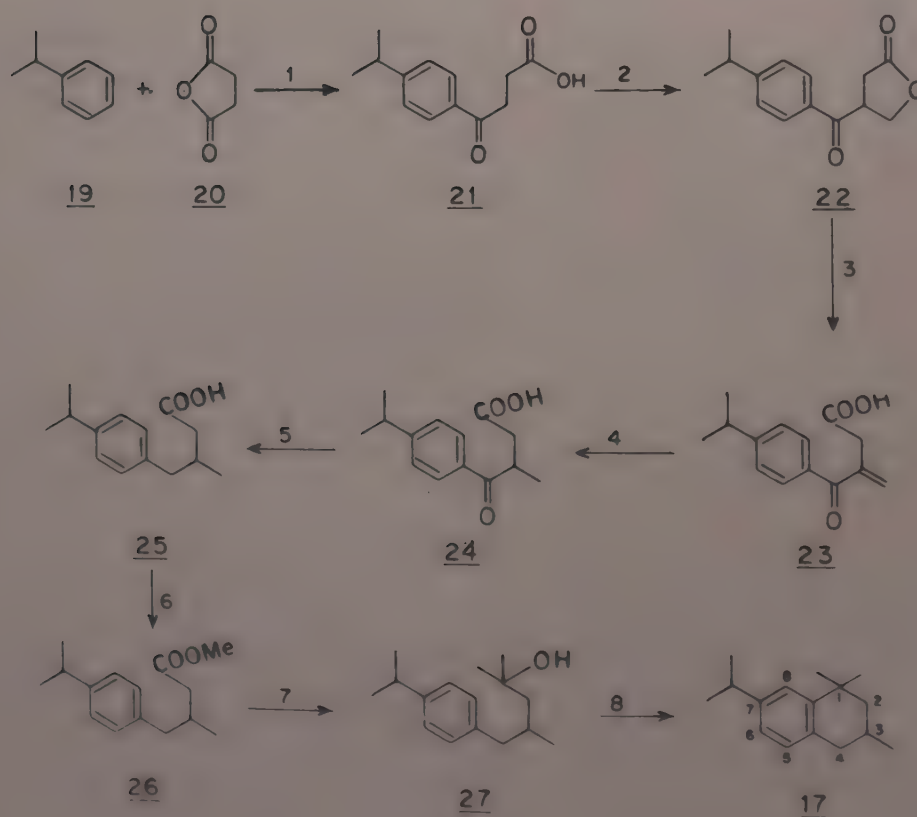
A mixture of 2 (1 g), dry toluene (20 ml) and  $\text{BF}_3 \cdot \text{OEt}_2$  (0.3 ml) was refluxed (17 hr), worked-up as usual and the product chromatographed on a column of  $\text{AgNO}_3$ -silica gel: Fr. 1, light petroleum, 2 × 25 ml, pure 18 (R = Me), colourless liquid, b.p. 130° (bath)/2 mm (0.2 g, 20%); IR (smear): featureless; PMR ( $\text{CCl}_4$ ):  $\delta$  0.85 to 1.00 (unresolved signals, 5 × 3H, comprising of two *t*-Me + one *s*-Me + one isopropyl); MS:  $m/z$  220 ( $\text{M}^+$ ) (Found: C, 87.1; H, 12.1.  $\text{C}_{16}\text{H}_{28}$  requires C, 87.3; H, 12.7%).

Fr. 2, light petroleum, 7 × 25 ml, 17 (R = Me), colourless liquid, b.p. 130° (bath)/0.6 mm (0.18 g, 18%);

reagent is invariably known<sup>8</sup> to react in such a way that the carbonyl group, farthest removed from the methyl, attaches to the aryl nucleus), the route depicted in Scheme 3 was followed to obtain the right tetralin (17, R = Me). The recently described<sup>9</sup> hydroxymethylation of 3-arylpropanoic acids after some optimization of the molar ratios of substrate/ $\text{CH}_2\text{O}$ / $\text{NaOH}$ , afforded 23; catalytic hydrogenation gave 24 with the required extra methyl at the right carbon. Clemmensen reduction of 24 followed by esterification yielded 26; dimethylation of the ester carbon of 26 by treatment with methyl lithium generated the tertiary carbinol 27 which, on exposure to polyphosphoric acid cyclized to give the desired 1,1,3-trimethyl-7-isopropyltetralin (17).



SCHEME 2



Reagents

1.  $\text{AlCl}_3 - \text{PhNO}_2$  2.  $\text{CH}_2\text{O} - \text{NaOH}$  3.  $\text{NaOMe} - \text{MeOH}$  4.  $\text{H}_2 / \text{PtO}_2 - \text{AcOH}$   
 5. Amalgamated  $\text{Zn} - \text{HCl} - \text{Toluene}$  6.  $\text{CH}_2\text{N}_2$  7.  $\text{MeLi}(\text{excess}) - \text{Et}_2\text{O}$  8.  $\text{PPA}$

SCHEME 3

IR (smear): 1620, 1505, 840, 820; PMR ( $\text{CDCl}_3$ ):  $\delta$  7.06 (s, 1H, Ar-H), 6.91 (perturbed AB "quartet" with  $\delta/J$  very small, 2H, ArH), 1.25 (d, 6H, isopropyl methyls,  $J = 5$  Hz), 1.26, 1.19 (s, 3H each, tertiary Me's), 1.03 (d, 3H, *s*-Me,  $J = 5$  Hz). MS:  $m/z$  216 ( $\text{M}^+$ ) (Found: C, 87.9; H, 11.4.  $\text{C}_{16}\text{H}_{24}$  requires C, 88.8; H, 11.2%).

*Synthesis of 1,1,3-trimethyl-7-isopropyltetralin (17, R = Me)*

3-(*p*-Isopropylbenzoyl)-propanoic acid (21) was prepared<sup>12</sup> by succinylation of cumene in nitrobenzene with anhydrous  $\text{AlCl}_3$  as the catalyst: m.p.  $134^\circ$ .

*(a) Hydroxymethylation of 21: Enone acid (23)*

Formalin (37% soln; 7.3 ml, 99 mmol) was added to a stirred solution of 21 (12.1 g, 55 mol) in 0.5N NaOH (176 ml, 99 mmol) (molar ratio of 21: HCHO:NaOH = 1:1.8:1.8). After 1 hr at room temperature, the mixture was acidified with conc. HCl (12 ml) and stirred overnight. The mixture was poured into water, extracted with ether ( $3 \times 100$  ml), washed with aq.  $\text{NaHCO}_3$ , brine, dried and solvent removed to get the crystalline lactone 22 (5.5 g, 46%), m.p.  $85^\circ$  (aq. ethanol); IR (nujol): 1770, 1675, 1605, 1235, 1015, 850. PMR ( $\text{CDCl}_3$ ):  $\delta$  7.69 (ABq, 4H, Ar-H,  $J = 6$  Hz), 4.56 (m, 2H,  $\text{O}=\text{C}-\text{O}-\text{CH}_2-$ ), 2.80 (m, 2H, benzylic CH and  $\text{O}=\text{C}-\text{CH}$ ), 1.28 (d,  $2 \times 3$ H, isopropyl Me's,  $J = 5$  Hz). (Found: C, 72.0; H, 7.1;  $\text{C}_{14}\text{H}_{16}\text{O}_3$  requires C, 72.4; H, 6.9%).

A mixture of 22 (5.5 g, 25 mmol) in 1% methanolic NaOMe (50 ml, 10 mmol) was stirred at room temp. for 15 min, acidified with dil. HCl, extracted with ether ( $2 \times 50$  ml) and the acid separated with 2% aq. NaOH. Acidification of the alkaline extract, extraction with ether ( $3 \times 50$  ml), washing with brine, drying, removal of solvent and distillation gave 23 (3.2 g, 60%), b.p.  $180^\circ/2$  mm; IR (smear): 1710, 1650, 1600, 1000, 855, 800; PMR ( $\text{CCl}_4$ ):  $\delta$  7.33 (ABq, 4H, Ar-H,  $J = 8$  Hz), 5.80, 5.60 (two s, 1H each,  $>\text{C}=\text{CH}_2$ ), 3.4 (s, 2H,  $\text{O}=\text{C}-\text{CH}_2\text{COOH}$ ), 2.9 (septet, 1H, benzylic H), 1.22 (d,  $2 \times 3$ H, isopropyl Me's,  $J = 8$  Hz). (Found: C, 71.0; H, 6.9.  $\text{C}_{14}\text{H}_{16}\text{O}_3$  requires C, 72.4; H, 6.9%).

*Methyl (4-isopropylphenyl)-3-methyl-butanoate (26) from 23*

A stirred solution of 23 (2 g) in AcOH (20 ml) was hydrogenated with Adams  $\text{PtO}_2$  catalyst (55 mg) when the dihydro derivative 24 (1.9 g) was obtained. This was subjected to Clemmensen reduction with amalgamated zinc (10 g), conc. HCl (10 ml), water (5 ml) and toluene (10 ml) at reflux temp. for 30 hr; conc. HCl (10 ml) was added at intervals of 6 hr. The crude product was chromatographed on a column of silica gel and the faster-moving pure 25 (0.8 g, 45%)

separated from the unwanted polar byproduct. Treatment of 25 with ethereal  $\text{CH}_2\text{N}_2$  and distillation afforded 26 as a colourless liquid, b.p.  $160^\circ$  (bath)/2 mm; IR (smear): 1745, 1520, 1210, 1160, 810; PMR ( $\text{CCl}_4$ ):  $\delta$  3.58 (s, 3H, COOMe), 1.23 (d,  $2 \times 3$ H, isopropyl Me's,  $J = 8$  Hz), 0.94 (d, 3H, *s*-Me,  $J = 5$  Hz); MS:  $m/z$  234 ( $\text{M}^+$ ) (Found: C, 77.2; H, 9.6.  $\text{C}_{15}\text{H}_{22}\text{O}_2$  requires C, 76.9; H, 9.5%).

*1,1,3-Trimethyl-7-isopropyltetralin (17) from 26*

26 (0.52 g) in dry ether (20 ml) was treated with excess MeLi (2 ml of 3 molar solution in ether) and stirred under  $\text{N}_2$  for 17 hr. The mixture was poured into cold water, the ether layer separated and the aqueous portion extracted with more ether. The combined organic extract was washed with brine, dried, solvent removed and the residue distilled to yield the carbinol (27, 0.35 g, 70%); IR (smear): 3400, 1150, 820; PMR ( $\text{CCl}_4$ ):  $\delta$  7.0 (s, 4H, Ar-H), 1.21 (d,  $2 \times 3$ H, isopropyl Me's,  $J = 6$  Hz), 1.13 (s,  $2 \times 3$ H, *t*-Me's), 0.91 (d, 3H, *s*-Me,  $J = 6$  Hz). Carbinol (27) (0.32 g) was treated with polyphosphoric acid (from 2.4 ml of  $\text{H}_3\text{PO}_4$  and 4.8 g of  $\text{P}_2\text{O}_5$ ) at  $100^\circ$  for 30 min, the mixture poured into ice-water, extracted with light petroleum and the residue distilled to afford 17 (0.2 g, 62%), the spectral data (IR/PMR) of which were identical with the tetralin derived from 2 by  $\text{BF}_3 \cdot \text{OEt}_2$  rearrangement.

**References**

- Goudgaon N M, Shitole H R & Nayak U R, *Indian J Chem*, **24B** (1985) 350.
- (a) Jadhav P K & Nayak U R, *J scient ind Res*, **39** (1980) 36; (b) Sukh Dev, *Prog Chim Org Nat Prod*, **40** (1981) 50; (c) Stehelin L, Lhomme J & Ourisson G, *J Am chem Soc*, **93** (1971) 1650.
- (a) Nayak U R & Sukh Dev, *Tetrahedron*, **8** (1960) 42; (b) Prahlad J R, Nayak U R & Sukh Dev, *Tetrahedron*, **26** (1970) 663.
- (a) Berson J A, Hammons J H, McRow A W, Bergman R G, Romanick A & Houston D, *J Am chem Soc*, **89** (1967) 2590; (b) Yadav J S, Nayak U R & Sukh Dev, *Tetrahedron*, **36** (1980) 309; (c) Yadav J S, Soman R, Sobti R R, Nayak U R & Sukh Dev, *Tetrahedron*, **36** (1980) 2105; (d) Shitole H R & Nayak U R, *Indian J Chem*, **22B** (1983) 215.
- (a) Ranganathan R, Nayak U R, Santhanakrishnan T S & Sukh Dev, *Tetrahedron*, **26** (1970) 621; (b) Beyler R E & Ourisson G, *J org Chem*, **30** (1965) 2838.
- Bisarya S C, Nayak U R & Sukh Dev, *Tetrahedron Lett*, (1969) 2323.
- Berliner E, *Org React*, **5** (1949) 229.
- (a) Rothstein E & Saboor M A, *J chem Soc*, (1943) 425; (b) Sukh Dev & Guha P C, *J Indian chem Soc*, **25** (1948) 13.
- Cignarilla G, Grella G & Curzu M M, *Synthesis*, (1980) 825.
- Fieser L F & Fieser M, *Reagents for organic synthesis*, Vol. 1, (John Wiley, New York), 1967, pp. 70.
- Gupta A S & Sukh Dev, *J Chromatog*, **12** (1963) 189.
- (a) Smith L I & Lo C P, *J Am chem Soc*, **70** (1948) 2209. (b) Farnum D G, Roger A M & Mehta G, *J Am chem Soc*, **95** (1973) 8692.

## A New Pregnane Glycoside from *Periploca calophylla*

DESH DEEPAK, MAHESHWARI P KHARE & ANAKSHI KHARE\*

Department of Chemistry, Lucknow University, Lucknow 226 007

Received 28 February 1985; accepted 21 June 1985

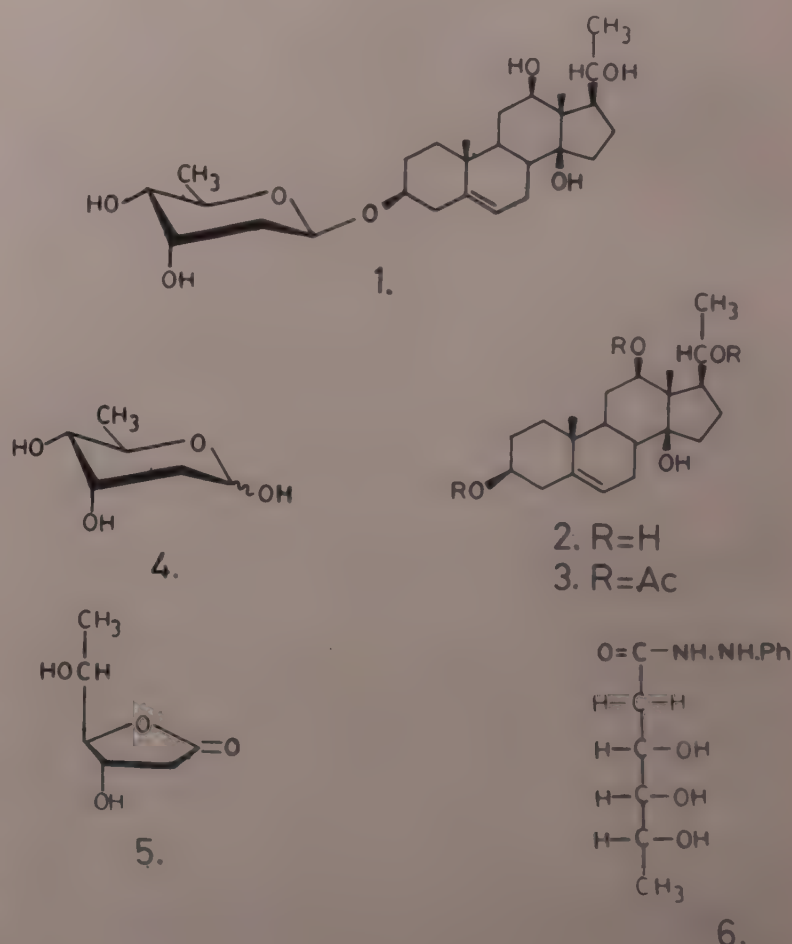
A pregnane glycoside of boucerin named locin has been isolated from the dried twigs of *Periploca calophylla*. On the basis of chemical and spectroscopic evidences, its structure has been established as boucerin-3-O- $\beta$ -D-digitoxose (1).

We have previously reported the isolation and structure elucidation of three novel glycosides plocin<sup>1</sup>, plocinin<sup>2</sup> and calocin<sup>3</sup> as well as triterpenoids<sup>4</sup> from the extract of *Periploca calophylla* (fam: Asclepiadaceae). The isolation and structure elucidation of yet another glycoside, designated as locin (1), from this plant material, are presented in this note.

Locin (1), m.p. 110-15°,  $[\alpha]_D^{25} + 20^\circ$  (MeOH),  $C_{27}H_{44}O_7$ , was isolated from the combined chloroform-ethanol (3:2) and (4:1) extracts of the twigs of *P. calophylla*. A positive Liebermann-Burchardt colour reaction<sup>5</sup>, characteristic colour tests for 2-deoxysugars in xanthydrol<sup>6</sup> (pink colour) and Keller-Kiliani<sup>7</sup> (blue colour) reactions indicated 1 to be a steroidal 2-deoxyglycoside. It underwent oxidation with  $NaIO_4$ . In the PMR spectrum of 1, presence of characteristic methylene signals in the regions  $\delta$  2.16-2.04 (1H) and 1.84-1.78 (1H) together with a secondary methyl doublet at  $\delta$  1.30 ( $J = 7$  Hz) provided evidence that 1 is a monoglycoside of 2,6-dideoxyhexose.

Mild acid<sup>8</sup> hydrolysis of 1 with 0.05 N  $H_2SO_4$  afforded a genin (2), m.p. 235-38°,  $[\alpha]_D^{25} - 4.2^\circ$  (MeOH),  $C_{21}H_{34}O_4$  and a chromatographically pure reducing sugar 4,  $[\alpha]_D^{25} + 40^\circ$  ( $H_2O$ ), identified as D-digitoxose<sup>9</sup> (2,6-dideoxyribohexose) by comparison with the authentic sample (PC,  $[\alpha]_D$ ). It gave pink colour in xanthydrol reaction and also underwent  $NaIO_4$  oxidation. Further evidence for the sugar residue was provided by the following experiment. 4 was reacted with bromine water to get the lactone (5) which with phenylhydrazine yielded the known D-digitoxonic acid phenylhydrazide<sup>9</sup> (m.p., m.m.p.).

The genin (2) did not react with  $NaIO_4$  unlike the glycoside (1) and sugar (4), indicating the absence of a vicinal diol group in the genin moiety. From the m.p. and specific rotation comparison, 2 appeared to be boucerin<sup>10</sup> (pregn-5-ene-3 $\beta$ , 12 $\beta$ , 14 $\beta$ , 20 $\beta$ -tetrol). This was further supported by the formation of a crystalline triacetate (3) (m.p. 19, 20 and 21, m.p. 145-46,  $C_{21}H_{34}O_4$ ) when 2 was subjected to acetylation using acetic anhydride and pyridine (lit.<sup>11</sup>).



The mass spectrum of 1 did not exhibit the  $M^+$  but gave ( $M^+ - \text{sugar}$ ) ion at  $m/z$  332 which showed further fragmentation giving peaks at  $m/z$  314 ( $M^+ - \text{sugar} - H_2O$ ), 269 ( $314 - CHO.H.CH_3$ ), 241 ( $269 - C_2H_4$ ), 254 ( $269 - CH_3$ ) and 236 ( $254 - H_2O$ ) indicating the presence of hydroxyl groups and a hydroxyethyl chain. The fragment ion peaks at  $m/z$  139, 121 and 106 involving rings A and B resulted from the cleavage<sup>11</sup> of C-9 and C-10 bond in 1. The other fragments of this cleavage involving rings B and C appeared at  $m/z$  211, 183, 168, 123 and 105. The cleavage of C-9 and C-11 bond of ring C<sup>12</sup> in 1 gave a fragment ion at  $m/z$  163 and its subsequent ion at  $m/z$  130 resulting from the loss of methyl radical and  $H_2O$  molecule from it. The prominent fragment ion peak at  $m/z$  97 originated from ring-D due to a fragmentation mode<sup>12</sup> initiated by the

hydroxyl group present at C-14. The mass spectrum of **1** also contained the common 2,6-dideoxyhexose fragments at  $m/z$  130, 113 and 95.

The 400 MHz PMR spectrum of the glycoside (**1**) not only provided an unequivocal confirmation of the derived structure, but also clearly defined the configuration of the glycosidic linkage. The splitting pattern of the anomeric proton as a double doublet at  $\delta$  4.97 ( $J=8$  and 3 Hz) indicated its axial configuration suggesting that the sugar unit was present in the  $^4C_1$  (D) conformation and linked to the aglycone through a  $\beta$ -glycosidic linkage. The three one-proton multiplets centered at  $\delta$  3.54, 3.36 and 3.23 could be assigned to H-5', H-3' and H-4' of the sugar moiety while the one-proton multiplets at  $\delta$  4.18 and 3.94 would evidently be the methine protons at C-17 and C-20 of the genin moiety, respectively. The chemical shift of a one-proton double doublet at  $\delta$  3.76 ( $J=8$  and 3 Hz) was assigned to C-12 methine proton.

On the basis of the preceding data it could be concluded that the structure of locin (**1**) is boucerin-3-*O*- $\beta$ -D-digitoxoside.

### Experimental Procedure

The general procedure were the same as those reported recently<sup>1</sup> except mass spectra were recorded on a AE-I-MS-30 mass spectrometer, and the 400 MHz PMR spectra (CDCl<sub>3</sub>) on a Bruker instrument.

#### Isolation of locin (**1**)

The shade-dried twigs (5 kg) of *P. calophylla* were extracted as reported earlier<sup>13</sup> yielding CHCl<sub>3</sub>–EtOH (4:1) extract (7 g) and CHCl<sub>3</sub>–EtOH (3:2) extract (5.2 g). These combined extracts on column chromatography yielded locin (**1**), yield 68 mg. (Found: C, 67.3; H, 9.0; C<sub>27</sub>H<sub>44</sub>O<sub>7</sub> requires C, 67.5; H, 9.1 %); PMR (400 MHz):  $\delta$  5.34 (1H, *m*, H-6), 4.97 (1H, *dd*,  $J=8$  and 3 Hz, H-1), 4.18 (1H, *m*, H-17), 3.94 (1H, *m*, H-20), 3.76 (1H, *dd*,  $J=8$  and 3 Hz, H-12), 3.54 (1H, *m*, H-5'), 3.36 (1H, *m*, H-3'), 3.23 (1H, *m*, H-4'), 2.16–2.04 (1H, *m*, H-2'e), 1.84–1.78 (1H, *m*, H-2'a), 1.64–1.58 (CH<sub>2</sub> of aglycone), 1.33 (3H, *d*,  $J=7$  Hz, 21-CH<sub>3</sub>), 1.30 (3H, *d*,  $J=7$  Hz, 6'-CH<sub>3</sub>), 1.06 (3H, *s*, 18-CH<sub>3</sub>), 0.97 (3H, *s*, 19-CH<sub>3</sub>); MS: molecular ion peak was not observed. Other peaks at  $m/z$  332 (M–sugar), 314 (332–H<sub>2</sub>O), 269 (314–CH<sub>3</sub>–CHOH), 241 (269–C<sub>2</sub>H<sub>4</sub>), 254 (269–CH<sub>3</sub>), 236 (254–H<sub>2</sub>O); genin fragments:  $m/z$  211 (genin–139), 183 (211–C<sub>2</sub>H<sub>4</sub>), 168 (183–CH<sub>3</sub>), 123 (168–CH<sub>3</sub>–CHOH), 105 (123–H<sub>2</sub>O), 139 (genin–211), 121 (139–H<sub>2</sub>O), 106 (121–CH<sub>3</sub>), 130 (163–H<sub>2</sub>O–CH<sub>3</sub>), 97; sugar fragments:  $m/z$  130, 113 and 95.

#### Mild hydrolysis of **1** with acid

A solution of **1** (20 mg) in 80% aq. 1,4-dioxane

(1.2 ml) was hydrolysed with 0.1N H<sub>2</sub>SO<sub>4</sub> (1.2 ml) at 50° for 30 min. The usual work-up afforded crystalline genin **2** (12 mg) (Found: C, 71.93; H, 9.68. C<sub>21</sub>H<sub>34</sub>O<sub>4</sub> requires C, 72.00, H, 9.71 %) and syrupy sugar **4** (5.5 mg).

#### Oxidation of **4** with bromine water

A solution of **4** (4 mg) in H<sub>2</sub>O (0.6 ml) was oxidised with bromine<sup>9</sup> (12  $\mu$ L) following the earlier method yielding syrupy lactone **5** (2.3 mg). It gave violet colouration with NH<sub>2</sub>OH–FeCl<sub>3</sub> reagent.

#### D-digitoxonic acid phenylhydrazide (**6**)

A solution of lactone **5** (2 mg) in absolute EtOH (0.05 ml) was heated with phenylhydrazine (0.05 ml) at 100° for 30 min usual work-up gave **6**, m.p. 121–23° (MeOH–Et<sub>2</sub>O), identical with D-digitoxonic acid phenylhydrazide (m.m.p., IR).

#### Acetylation of **2**

Compound **2** (5 mg) on acetylation with Ac<sub>2</sub>O (0.5 ml) in C<sub>5</sub>H<sub>5</sub>N (0.5 ml) at 100° for 9 hr and usual work-up afforded a crystalline triacetate **3** (5 mg), m.p. 145–46° (Found: C, 68; H, 8.32. C<sub>27</sub>H<sub>40</sub>O<sub>7</sub> requires C, 68.06; H, 8.40 %); PMR (80 MHz-FT):  $\delta$  2.1 (3H, *s*, OAc), 2.0 (3H, *s*, OAc), 1.90 (3H, *s*, OAc).

### Acknowledgement

The authors thank Dr D K Kulshreshtha of CDRI, Lucknow for helpful discussion.

### References

- 1 Desh Deepak, Khare M P & Khare A, *Phytochemistry*, **24** (1985) 1037.
- 2 Desh Deepak, Khare M P & Khare A (1985), *Phytochemistry*, (accepted).
- 3 Srivastava O P, Khare A & Khare M P, *J nat Prod*, **45** (1982) 211.
- 4 Srivastava O P, Khare A & Khare M P, *J nat Prod*, **46** (1983) 458.
- 5 Abisch E & Reichstein T, *Helv chim Acta*, **43** (1960) 1844.
- 6 (a) Barton G M, Evans R S & Gardner J A F, *Nature (London)*, **170** (1952) 249.  
(b) Tschesche R, Grimmer G & Seehofer F, *Chem Ber*, **86** (1953) 1235.
- 7 Nagata W, Tamm Ch & Reichstein T, *Helv chim Acta*, **40** (1957) 41.
- 8 Rangaswami S & Reichstein T, *Helv chim Acta*, **32** (1949) 939.
- 9 Eppenberger U, Kaufmann H, Stocklin W & Reichstein T, *Helv Chim Acta*, **49** (1966) 1492.
- 10 Nikaido H, Shimizu Z & Mitsuhashi H, *Chem Pharm Bull*, **15** (1967) 725.
- 11 Budzikiewicz H, Djerassi C & Williams D H, *Structure elucidation of natural products by mass spectrometry*, Vol. II (Holden-Day, New York) 1964.
- 12 Fukuoka M, Hayashi K & Mitsuhashi H, *Chem Pharm Bull*, **19** (1971) 1469.
- 13 Bailly P R O, Mohar K & Reichstein T, *Helv chim Acta*, **45** (1954) 315.

## Synthesis of (1 *RS*, 7 *SR*, 8a *RS*)-1,2,3,5,6,7,8,8a-Octahydro-4,7-dimethyl-1-naphthoic Acid & Its Reaction with Lead Tetraacetate†

K SHANKARAN, D G TALEKAR, A S VAIDYA & A S RAO\*

National Chemical Laboratory, Pune 411 008

Received 20 June 1984; accepted 10 May 1985

Thermal addition of ethyl acrylate to *p*-mentha-3, 8(9)-diene (**1**) furnishes predominantly a mixture of adducts, ethyl (1 *RS*, 7 *SR*, 8a *RS*)-1, 2, 3, 5, 6, 7, 8, 8a-octahydro-4, 7-dimethyl-1-naphthoate (**5**) and ethyl (1 *SR*, 7 *SR*, 8a *SR*)-1, 2, 3, 5, 6, 7, 8, 8a-octahydro-4, 7-dimethyl-1-naphthoate (**17**). An acid prepared via Diels-Alder reaction of **1** with ethyl acrylate has been assigned the structure **4** on the basis of X-ray studies. Another acid isolated in the Diels-Alder reaction has been assigned the structure (**18**) on the basis of <sup>13</sup>C NMR of its methyl ester (**19**) and the PMR spectrum of the iodolactone (**21**) derived from it. Decarboxylation of **4** with lead tetraacetate furnishes a mixture of 1, 6-dimethyl-5, 6, 7, 8-tetrahydronaphthalene (**22**), (1 *RS*, 7 *SR*, 8a *RS*)-1, 2, 3, 5, 6, 7, 8, 8a-octahydro-4, 7-dimethyl-1-naphthalenyl acetate (**7**) and the lactone (**10**). The addition of vinyl acetate to **1** furnishes the acetate (**7**) along with other products.

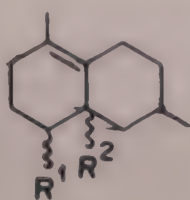
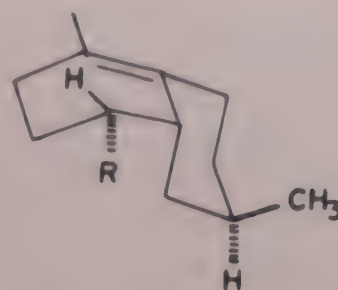
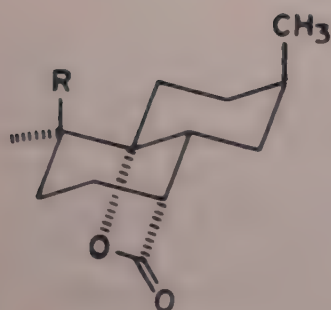
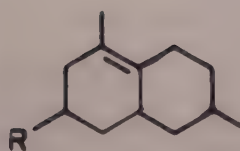
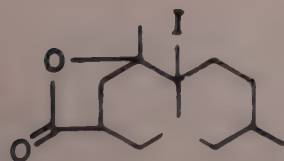
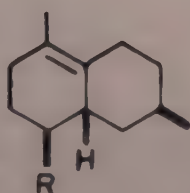
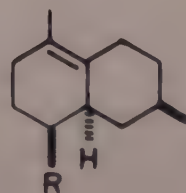
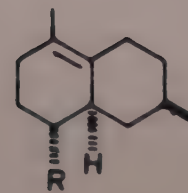
We have earlier examined the action of lead tetraacetate on a number of organic acids<sup>1-3</sup>. As an extension, we report herein the synthesis of the title acid (**4**) and its reaction with lead tetraacetate. This investigation has provided a route for the preparation of the homoallylic alcohol (**8**). It is of interest to note that homoallylic and homobenzylic alcohols are useful intermediates in organic synthesis since they undergo fragmentation reactions<sup>4,5</sup>.

The Diels-Alder reaction of the diene (**1**) with methyl acrylate was studied by Buttery and Ling<sup>6</sup> but they did not examine the stereochemistry of the products obtained. The reaction of the diene (**1**) with acrolein has been shown<sup>7</sup> to furnish a mixture of the aldehydes (**2**) and (**3**), but none of their regioisomers. We have reinvestigated the reaction of **1** with ethyl acrylate. GLC studies show the formation of two major and two minor adducts. When the mixture of adducts is saponified and transformed to the corresponding mixture of acids it is observed that one of the acids can be readily purified via recrystallization from petroleum ether. X-ray crystallographic studies have shown<sup>8</sup> that the crystalline acid, m.p. 154-55° has the stereochemistry **4** and the C-7 methyl is axial. The presence of an axial CH<sub>3</sub> in **4** is also supported by the <sup>13</sup>C NMR spectrum of the methyl ester (**6**), m.p. 56-57°, the purity of which was ascertained by GLC. Ester (**6**) must have been obtained along with other adducts by Buttery and Ling<sup>6</sup>. The <sup>13</sup>C NMR spectrum of **6** exhibits a signal at δ 20.7 assignable to axial methyl carbon<sup>9</sup>. The absence of signal around δ 23.5 indicates the absence of an

equatorial methyl group<sup>9</sup>. On treatment with iodine in the presence of sodium bicarbonate, **4** is readily transformed to an iodolactone, the stereochemistry **9** for which is based on literature analogy<sup>10</sup>, and is supported by the spectral data.

After removing **4** from the mixture of acids, the mother liquor furnished an acid which has been assigned the structure (**18**) on the following grounds. On treatment with sodium bicarbonate and iodine this acid furnishes a  $\gamma$ -lactone (IR band at 1780 cm<sup>-1</sup>). The signal pattern (four equally spaced signals) for CH-CO in the PMR spectrum of the lactone is comparable to that of CH-CO in **9**. This observation rules out the regiochemistry **13** for the iodolactone and the regiochemistry **12** for the acid, since the CH-CO in **13** can couple with four protons located on neighbouring carbons, in contrast to only three protons in the case of **9** and other lactones having the same regiochemistry as **9**. The <sup>13</sup>C NMR spectrum of the methyl ester (**19**) derived from the acid displays a signal at δ 23.9 due to equatorial methyl carbon at C-7 thus ruling out the stereochemistry **15** for the acid. Hence the acid obtained from the mother liquor must be **18** or **20a**. Though the data obtained by us do not allow a choice to be made, the structure **18** is to be preferred by analogy<sup>7,11</sup> with related Diels-Alder studies<sup>7,11</sup>. Endo addition will result in the formation of **17**.

The acid (**4**) was subjected to decarboxylation with lead tetraacetate in benzene in the presence of pyridine. The major products formed in the reaction were separated by column chromatography. The fraction which eluted first was identified as the hydrocarbon (**22**) on the basis of its PMR spectrum and elemental

12  $R^1 = \beta\text{-CHO}$ ;  $R^2 = \alpha\text{-H}$ 3  $R^1 = \alpha\text{-CHO}$ ;  $R^2 = \beta\text{-H}$ 4  $R = \text{CO}_2\text{H}$ 5  $R = \text{CO}_2\text{C}_2\text{H}_5$ 6  $R = \text{CO}_2\text{CH}_3$ 7  $R = \text{OCOCH}_3$ 8  $R = \text{OH}$ 9  $R = \text{I}$ 10  $R = \text{OCOCH}_3$ 11  $R = \text{CO}_2\text{C}_2\text{H}_5$ 12  $R = \text{CO}_2\text{H}$ 1314  $R = \text{CO}_2\text{C}_2\text{H}_5$ 15  $R = \text{CO}_2\text{H}$ 16  $R = \text{CO}_2\text{CH}_3$ 17  $R = \text{CO}_2\text{C}_2\text{H}_5$ 18  $R = \text{CO}_2\text{H}$ 19  $R = \text{CO}_2\text{CH}_3$ 20  $R = \text{CO}_2\text{C}_2\text{H}_5$ 20a  $R = \text{CO}_2\text{H}$ 20b  $R = \text{CO}_2\text{CH}_3$ 

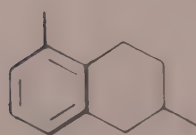
analyses (see Experimental). The decarboxylation of secondary acids with lead tetraacetate normally furnishes<sup>12</sup>, in minor quantities, the oxidative elimination products and hence the formation of hydrocarbons (23) and (24) may be anticipated. Cyclohexadienes are known to undergo facile oxidation to the corresponding arenes with lead tetraacetate and it is suggested that the hydrocarbon (22) is formed via a mixture of 23 and 24. The other products formed in the decarboxylation of 4 were identified as the homoallylic acetate (7) and the lactone (10) on the basis of spectral data and elemental analyses. Saponification of 7 furnished the alcohol (8).

Since the yield of 7 is not very high due to the formation of side products (10 and 22), we have

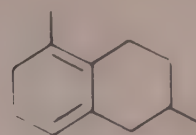
examined the Diels-Alder reaction involving the diene 1 and vinyl acetate. One of the components formed in the reaction is a dimer (31 and/or 32) of diene 1. The more polar fraction isolated via chromatography is a mixture of acetates; one of the components of this mixture has been shown by GLC to be the acetate (7). However, PMR spectrum and GLC behaviour indicate that other stereoisomeric and regioisomeric (26) acetates are also formed; hence this route is less efficient than the decarboxylation route for the preparation of 7. The Diels-Alder reaction of the diene (28) with vinyl acetate has been studied by Wharton and coworkers<sup>13</sup> who have shown that a mixture of regioisomers (25) and (27) is formed; however, they have not reported the formation of dimer from 28.



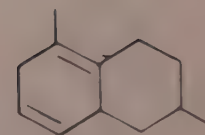
21 R = I



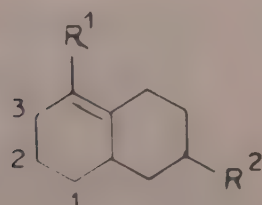
22



23



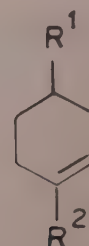
24



25  $R^1 = R^2 = H$ , OAc at C-2

26  $R^1 = R^2 = CH_3$ ; OAc at C-2

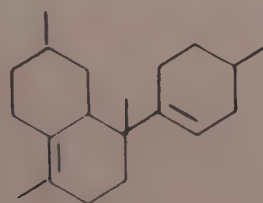
27  $R^1 = R^2 = H$ ; OAc at C-1



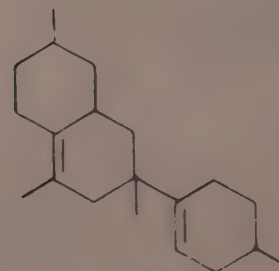
28  $R^1 = H$ ,  $R^2 = CH=CH_2$

29  $R^1 = CH_3$ ;  $R^2 = CO_2H$

30  $R^1 = CH_3$ ,  $R^2 = -C(CH_3)_2OH$



31



32

Since the diene (**1**) is a key intermediate for the preparation of **4**, we have critically examined several routes for its preparation. An excellent method for the preparation of **1** involves heating the tertiary allylic alcohol (**30**) with pyridine-alumina according to a procedure developed by von Rudloff<sup>16</sup>.

### Experimental Procedure

Racemic diene (**1**) was employed and hence all the compounds reported are racemates. GLC studies were carried out on Hewlett Packard 5730 instrument fitted with flame ionisation detector. The carrier gas was nitrogen and the flow rate was 30 ml/min. The column was 1.8 m long having an internal diameter of 2 mm. The stationary phase was a mixture of 1.5% OV-101 and 1.5% OV-17 impregnated on Chromosorb W-HP as stationary phase.

#### *p*-Menthyl-3-(9)-diene (**1**)

The acid (**29**) prepared<sup>18</sup> from 4-methylcyclohexanone, was transformed to the alcohol (**30**) according to

the literature procedure<sup>16</sup>. The alcohol (**30**, 10 g) was added to an intimate mixture of alumina (19.6 g) and pyridine (0.4 g) in a distillation flask. The distillation flask was immersed in a bath maintained at 300-320°. The distillate was extracted with ether, washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). The residue obtained after removal of solvent was distilled to furnish **1** (8 g), b.p. 125° (bath)/40 mm (lit.<sup>17</sup> b.p. 105°/20 mm).

#### (1 *RS*, 7 *SR*, 8a *RS*)-1,2,3,5,6,7,8,8a-Octahydro-4,7-dimethyl-1-naphthoic acid (**4**)

A mixture of diene **1** (5.4 g), ethyl acrylate (6.3 g) and hydroquinone (0.2 g) was heated under nitrogen atmosphere at 90° for 48 hr. The reaction mixture was fractionated using a vigreux column and the fraction, b.p. (bath) 145°/3.5 mm (5.5 g) was collected. GLC examination of this fraction at 150° showed four peaks with retention times of 11.19, 12.42, 14.64 and 16.34 min and the peak areas were in the ratio 7.40:46.7. This fraction analysed for C<sub>17</sub>H<sub>24</sub>O<sub>2</sub> (found: C, 76.3; H, 10.4. C<sub>17</sub>H<sub>24</sub>O<sub>2</sub> requires C, 76.2; H, 10.2%). A mixture

of the above fraction (4.4 g), methanol (40 ml), sodium hydroxide (0.8 g) and water (3.5 ml) was heated under reflux for 6 hr. After removing the methanol *in vacuo* the residue was diluted with water, extracted with ether to remove non-acidic material, the aqueous layer acidified and extracted with ether to remove non-acidic material, the aqueous layer acidified and extracted with ether. The ether extract was washed with water, dried and the solvent evaporated. Recrystallization of the residue from petroleum ether furnished **4** (1.5 g). A sample for X-ray crystallography and elemental analyses was obtained by two recrystallizations from pet. ether, m.p. 154-55° (Found: C, 75.0; H, 9.6.  $C_{13}H_{20}O_2$  requires C, 75.0; H, 9.7%).

*Methyl (1 RS, 7 SR, 8a RS)-1,2,3,5,6,7,8,8a-octahydro-4,7-dimethyl-1-naphthoate (6)*

Esterification of **4** with diazomethane furnished **6** (yield, 95%), m.p. 56-57°; IR (nujol):  $1735\text{ cm}^{-1}$  (C=O); PMR (60 MHz,  $CCl_4$ ):  $\delta$  1.03 (3H, *d*,  $J=6\text{ Hz}$ ,  $CH_3-CH$ ), 1.6 (3H,  $CH_3-C=C$ ), 3.57 (3H, *s*,  $-OCH_3$ ).  $^{13}C$  NMR (22.6 MHz,  $CDCl_3$ ):  $\delta$  18.7, 18.9, 20.7, 26.0, 28.0, 31.7, 33.5, 34.4, 36.1, 44.1, 51.3, 123.2, 133.4, 175.6. The sample was homogeneous (GLC: retention time = 3.95 min with column temperature 180°) (Found: C, 75.4; H, 9.8.  $C_{14}H_{22}O_2$  requires C, 75.6; H, 10.0%).

*(1 RS, 4 RS, 4a RS, 7 SR, 8a RS)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-4,7-dimethyl-4a-hydroxy-4-iodo-1-naphthoic acid lactone (9)*

A mixture of **4** (0.16 g), aq. sodium bicarbonate (0.5 M, 5 ml), iodine (0.32 g), potassium iodide (1.33 g) and water (3 ml) was stirred in the dark at 25° for 24 hr, diluted with water and extracted with ether. The ether extract was washed with aq. sodium thiosulphate, water, dried, evaporated *in vacuo* and recrystallized from pet. ether to furnish **9** (0.26 g), m.p. 92°. IR (nujol):  $1785\text{ cm}^{-1}$  ( $\gamma$ -lactone); PMR (60 MHz,  $CCl_4$ ):  $\delta$  1.1 (3H, *d*,  $J=6\text{ Hz}$ ,  $CH_3-CH$ ), 2.0 (3H, *s*,  $CH_3-CI-$ ), 2.96 (1H, *q*,  $J=6\text{ Hz}$ ,  $-CH-CO$ ) (Found: C, 46.6; H, 5.6.  $C_{13}H_{19}IO_2$  requires C, 46.7; H, 5.4%).

*Oxidative decarboxylation of acid (4)*

A mixture of **4** (0.7 g), lead tetraacetate (3.1 g), pyridine (0.56 g) and benzene (15 ml) was heated under reflux for 6 hr cooled and the excess of lead tetraacetate destroyed by adding ethylene glycol. The benzene layer was washed with aq. sodium bicarbonate, water and dried. The residue obtained after removal of solvent was distilled initially at 25 mm and subsequently at 1 mm, raising the bath temperature to 220° towards the end to furnish 0.45 g of the distillate. The distillate was chromatographed on a column of alumina (grade II, 14 g), eluting the column successively with (i) pet. ether,

(ii) pet. ether + ethyl acetate (97:3), (iii) pet. ether + ethyl acetate (95:5) and (iv) pet. ether + ethyl acetate (93:7). Fraction (i) eluted was identified as 1,6-dimethyl-5,6,7,8-tetrahydronaphthalene (**11**) (0.08 g), b.p. (bath) 165 / 35 mm; IR (film): 1600, 1460,  $763\text{ cm}^{-1}$ ; PMR (60 MHz,  $CCl_4$ ):  $\delta$  1.04 (3H, *d*,  $J=6\text{ Hz}$ ,  $CH_3-CH$ ), 2.2 (3H, *s*,  $Ar-CH_3$ ), 2.63 (4H, *m*,  $Ar-CH_2$ ), 6.88 (3H, *s*,  $Ar-H$ ) (Found: C, 90.0; H, 10.1.  $C_{12}H_{16}$  requires C, 89.8; H, 10.1%). Fraction (ii) was identified as the acetate (**7**) (0.20 g); b.p. (bath) 125°/2.5 mm; IR (film):  $1740, 1235\text{ cm}^{-1}$  ( $CH_3-CO-O$ ); PMR (60 MHz,  $CCl_4$ ):  $\delta$  1.03 (3H, *d*,  $J=6\text{ Hz}$ ,  $CH_3-CH$ ), 1.6 (3H, *bs*,  $CH-C=C$ ), 2.0 (3H, *s*,  $CH_3-CO-O$ ), 4.5 (1H, *m*,  $-CHOAc$ ) (Found: C, 75.8; H, 9.9.  $C_{14}H_{22}O_2$  requires C, 75.6; H, 10.0%). Fraction (iii) was identified as (1 RS, 4 RS, 4a RS, 7 SR, 8a RS)-1,2,3,4,4a,5,6,7,8,8a-decahydro-4-acetoxy-4,7-dimethyl-4a-hydroxy-1-naphthoic acid lactone (**10**) (0.07 g). IR (film):  $1770$  ( $\gamma$ -lactone),  $1740\text{ cm}^{-1}$  ( $CH_3-CO-O-$ ); PMR (60 MHz,  $CCl_4$ ):  $\delta$  1.0 (3H, *d*,  $J=6\text{ Hz}$ ,  $CH_3-CH$ ), 1.5 (3H, *s*,  $CH_3-C-O$ ), 2.0 (3H, *s*,  $CH_3-CO-O$ ) (Found: C, 67.5; H, 8.4.  $C_{15}H_{22}O_4$  requires C, 67.6; H, 8.3%).

*(1 RS, 7 SR, 8a RS)-1,2,3,5,6,7,8,8a-Octahydro-4,7-dimethyl-1-naphthalenol (8)*

A mixture of **7** (0.14 g), sodium hydroxide (0.24 g), methanol (3 ml) and water (0.4 ml) was heated under reflux for 3 hr, diluted with water and extracted with ether. The ether extract was washed with water, dried, the solvent evaporated and the residue distilled to furnish **8** (0.099 g), b.p. (bath) 140°/0.5 mm; IR (film):  $3450\text{ cm}^{-1}$  (OH); PMR (60 MHz,  $CCl_4$ ):  $\delta$  1.1 (3H, *d*,  $J=6\text{ Hz}$ ,  $CH_3-CH$ ), 1.66 (3H, *bs*,  $CH_3-C=C$ ), 2.9 (1H, *bm*, OH, exchangeable with  $D_2O$ ) and 3.3 (1H, *m*,  $-CH$  (OH)) (Found: C, 79.7; H, 11.1.  $C_{12}H_{16}O$  requires C, 79.9; H, 11.2%).

*Methyl (1 SR, 7 SR, 8a SR)-1,2,3,5,6,7,8,8a-octahydro-4,7-dimethyl-1-naphthoate (19)*

The mixture of adducts prepared by reacting **1** with ethyl acrylate was saponified to give a mixture of four acids, a portion of which was esterified with diazomethane. The resulting methyl esters on GLC examination at 180° exhibited four peaks with retention times of 3.10, 3.50, 3.95 and 4.36 min and the peak areas in the ratio 7:40:46:7.

Recrystallization of the mixture of acids from methanol furnished a mixture of two acids, m.p. 134-36°. The methyl esters prepared from the acid mixture (m.p. 134-36°) exhibited only two peaks (GLC; 180°) with retention times of 3.50 and 3.95 min. When the acid mixture (m.p. 134-36°) was recrystallized from pet. ether the acid (**4**) separated out. Most of the acid (**4**) was removed by repeated cooling and filtration to furnish a

filtrate composed predominantly of acid (18) which was esterified with diazomethane. Purification of the resulting methyl ester through preparative TLC furnished the methyl ester (19) in 90% purity (GLC);  $^{13}\text{C}$  NMR (22.6 MHz,  $\text{CDCl}_3$ );  $\delta$  18.0, 18.9, 23.9, 26.1, 27.6, 31.6, 32.3, 34.6, 39.7, 48.4, 51.6, 123.7, 131.7, 177.0 (Found: C, 75.4; H, 9.9.  $\text{C}_{14}\text{H}_{22}\text{O}_2$  requires C, 75.6; H, 10.0%).

(1 SR, 4 SR, 4a SR, 7 SR, 8a SR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-4,7-dimethyl-4a-hydroxy-4-iodo-1-naphthoic acid lactone (21)

Acid 18 (~90% pure) prepared via saponification of 19, was reacted with sodium bicarbonate-iodine-potassium iodide as described for 9. The iodolactone obtained was purified through preparative TLC to furnish the lactone (21); IR:  $1780\text{ cm}^{-1}$ ; PMR (80 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.90 (3H, d,  $J=6\text{ Hz}$ ), 2.02 (3H, s,  $\text{CH}_3-\text{Cl}$  -), 2.97 (1H, q,  $J=6\text{ Hz}$ ,  $-\text{CH}-\text{CO}$ ).

Addition of vinyl acetate to *p*-mentha-3,8(9)-diene (1)

A mixture of 1 (4.8 g), vinyl acetate (3 g) and hydroquinone (0.15 g) was heated at  $190^\circ$  for 72 hr in a sealed tube. Unreacted vinyl acetate was distilled out on a steam-bath, the residue chromatographed on a column of alumina (grade II, 150 g), eluting the column successively with (i) pet. ether and (ii) pet. ether + ethyl acetate (95:5). Fraction (i) was the hydrocarbon (31

and/or 32) (1.3 g), b.p. (bath)  $145^\circ/0.15\text{ mm}$ ; PMR (60 MHz,  $\text{CCl}_4$ ): 0.77-1.1 (9H, m,  $\text{CH}_3$ ), 1.6 (3H, bs,  $\text{CH}_3-\text{C}=\text{C}$ ), 1.9-2.2 (9H, m, allylic  $\text{CH}_2$  and CH), 5.2 (1H, m, vinyl H) (Found: C, 88.0; H, 11.8.  $\text{C}_{20}\text{H}_{32}$  requires C, 88.2; H, 11.8%). Fraction (ii) (1.7 g), b.p. (bath)  $100^\circ/0.4\text{ mm}$  was a mixture containing, as one of the components, the acetate (7) (GLC); IR (film):  $1740\text{ cm}^{-1}$ .

## References

- 1 Vaidya A S, Dixit S M & Rao A S, *Tetrahedron Lett*, (1968) 5173.
- 2 Sane P P, Divakar K J & Rao A S, *Synthesis*, (1973) 541.
- 3 Divakar K J, Sane P P & Rao A S, *Tetrahedron Lett*, (1974) 399.
- 4 Shankaran K & Rao A S, *Indian J Chem*, **18B** (1979) 507.
- 5 Shankaran K, Talekar D G & Rao A S, *Synth Commun*, **12** (1982) 141.
- 6 Buttery R G & Ling L C, *J agric Fd Chem*, **25** (1977) 291.
- 7 Andersen N H, Ladner D W & Moone A L, *Synth Commun*, **8** (1978) 437.
- 8 Dhaneshwar N N, Tavale S S, Acharya K R & Guru Row T N, *Acta Cryst*, **C40** (1984) 1914.
- 9 Stothers J B, *Carbon-13 NMR spectroscopy* (Academic Press, New York), 1972, 66.
- 10 van Tamelen E E & Shamma M, *J Am chem Soc*, **76** (1954) 2315.
- 11 Sauer J, *Angew Chem internat Edn*, **6** (1967) 16.
- 12 Sheldon R A & Kochi J K, *Organic reactions*, **19** (1972) 279.
- 13 Wharton P S & Aw B T, *J org Chem*, **31** (1966) 3787.
- 14 von Rudloft E, *Can J Chem*, **39** (1961) 1860.
- 15 Qudrat-I-Khuda M & Ghosh S K, *J Indian chem Soc*, **17** (1940) 19.
- 16 Perkin W H, *J chem Soc*, **87** (1905) 647.
- 17 Chou T Q & Perkin W H, *J chem Soc*, **99** (1911) 537.

## Acid-catalysed Condensation of Isoprene with $\beta$ -Orcinaldehyde: Synthesis of 2,2-Dimethylformylchromans & Synthesis of 5-Methylxanthyletin & Seselin Derivatives

V K AHLUWALIA\* & RANJNA GUPTA†

Department of Chemistry, University of Delhi, Delhi 110 007

Received 23 May 1985; accepted 29 July 1985

Condensation of  $\beta$ -orcinaldehyde with isoprene in the presence of orthophosphoric acid gives 6-formyl-5-hydroxy-2,2,7-trimethyl-3,4-dihydro-2H-1-benzopyran (3), 6-formyl-7-hydroxy-2,2,5-trimethyl-3,4-dihydro-2H-1-benzopyran (4) and 6-formyl-2,2,5,8,8-pentamethyl-3,4,9,10-tetrahydro-2H,8H-benzo[1,2-*b*:3,4-*b'*]dipyran (2). The formylchroman (3) has been used for the synthesis of 5-methylseselin (6) and 5-methyl-3-phenylseselin (9) by Perkin condensation followed by dehydrogenation of the formed dihydroseselin with DDQ or NBS. A convenient synthesis of linear pyranocoumarins, viz. 5-methylxanthyletin (11) and 5-methyl-3-phenylxanthyletin (12) is also described. This involves blocking the more reactive 3-position of  $\beta$ -orcinaldehyde with iodine followed by condensation with isoprene. The iodochroman (13) thus formed, on Perkin condensation with acetic anhydride and sodium acetate or sodium phenylacetate gives 8-iodo-5-methyldihydroxanthyletin (15)/8-iodo-5-methyl-3-phenyldihydroxanthyletin (17) which on treatment with Zn-HCl furnish 5-methyldihydroxanthyletin (16)/5-methyl-3-phenyldihydroxanthyletin (18). Dehydrogenation of 16 and 18 with DDQ or NBS furnish the required xanthyletin (11) and (12) respectively.

2,2-Dimethylchromans are of rare occurrence in plants, but these are obtained as degradation products during the structure elucidation of naturally occurring phenolic products having isoprenoid unit<sup>1</sup>. The utility of these chromans as synthetic precursors has been well demonstrated<sup>2,3</sup>. In view of this, the condensation of  $\beta$ -orcinaldehyde (1) with 2-methylbut-1,3-diene(isoprene) in the presence of orthophosphoric acid has now been studied. This reaction results in the exclusive formation of 2,2-dimethylchromans in good yields as compared to those obtained in some earlier methods<sup>4-6</sup> of their synthesis. Pyranocoumarins have been reported to show marked physiological activities<sup>7-9</sup>. In this paper we also report a new and convenient route for the synthesis of 5-methylxanthyletin and seselin derivatives.

Condensation of 1 with isoprene in the presence of orthophosphoric acid gave a mixture of three products (A, B and C) in the ratio of 1:8:6 (overall yield 60%). These were separated by column chromatography on silica gel.

The slowest moving compound-C gave a negative ferric reaction but a positive DNP test and its elemental analyses showed the incorporation of two isoprene units. Its PMR data were compatible with the structure 6-formyl-2,2,5,8,8-pentamethyl-3,4,9,10-tetrahydro-2H,8H-benzo[1,2-*b*:3,4-*b'*]dipyran (2).

Both the compounds-A and B gave positive ferric reaction and their elemental analyses showed the

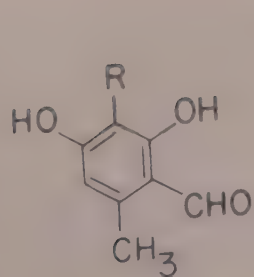
introduction of one isoprene unit. On the basis of similarity of PMR data the compounds-A and B could be either the angular chroman, viz., 6-formyl-5-hydroxy-2,2,7-trimethyl-3,4-dihydro-2H-[1]benzopyran (3) or the linear chroman, 6-formyl-7-hydroxy-2,2,5-trimethyl-3,4-dihydro-2H-[1]benzopyran (4). Structures of compounds A and B as 4 and 3 respectively were established by their further reaction with isoprene. In contrast to compound-B, which was recovered unchanged on reaction with isoprene, compound-A afforded 2 (compound-C).

Perkin condensation of 3 with acetic anhydride in the presence of sodium acetate gave 5,8,8-trimethyl-9,10-dihydro-2H,8H-benzo[1,2-*b*:3,4-*b'*]dipyran-2-one (5-methyldihydroseselin) (5). Its dehydrogenation with DDQ or NBS gave 5,8,8-trimethyl-2H,8H-benzo[1,2-*b*:3,4-*b'*]dipyran-2-one (5-methylseselin) (6), identical with an authentic sample obtained from 7-hydroxy-5-methylcoumarin (7).

Similarly 5,8,8-trimethyl-3-phenyl-2H,8H-benzo[1,2-*b*:3,4-*b'*]dipyran-2-one (5-methyl-3-phenylseselin) (9) was obtained by the Perkin condensation of 3 with acetic anhydride in presence of sodium phenylacetate followed by dehydrogenation of the formed 5,8,8-trimethyl-3-phenyl-9,10-dihydro-2H,8H-benzo[1,2-*b*:3,4-*b'*]dipyran-2-one (5-methyl-3-phenyldihydroseselin) (10).

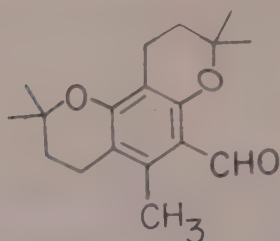
The linear formylchroman (4), required as intermediate for the synthesis of linear pyranocoumarins was obtained in very poor yield (4%). A convenient method has now been developed for the

\*Working as a Pool Officer (CSIR).

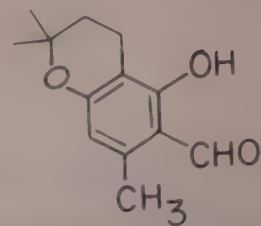


1, R = H

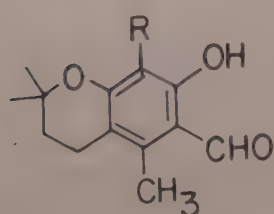
13, R = I



2

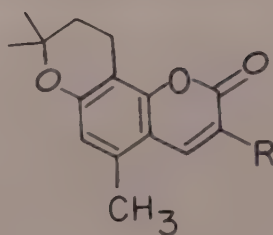


3



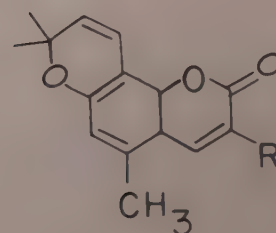
4, R = H

14, R = I



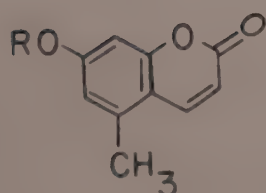
5, R = H

10, R = Ph

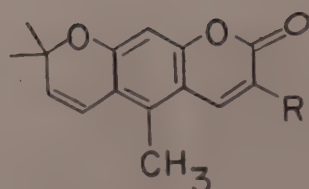


6, R = H

9, R = Ph

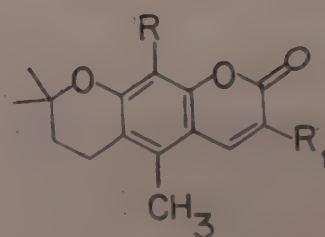


7, R = H

 8, R =  $\text{X} \equiv$ 


11, R = H

12, R = Ph


 R      R<sub>1</sub>

15,    I      H

16,    H      H

17,    I      Ph

18,    H      Ph

synthesis of linear pyranocoumarins, viz. 2,2,5-trimethyl-2H,8H-benzo[1,2-*b*:5,4-*b'*]dipyrans-8-one (5-methylxanthyletin) (11) and 2,2,5-trimethyl-7-phenyl-2H,8H-benzo[1,2-*b*:5,4-*b'*]dipyrans-8-one (5-methyl-3-phenylxanthyletin) (12). Thus iodination of 1 with iodine and periodic acid gave a product which was formulated as 2,4-dihydroxy-3-iodo-6-methylbenzaldehyde (13) in analogy with literature reports<sup>1,2,3</sup>. Condensation of 13 with isoprene in presence of orthophosphoric acid gave 6-formyl-7-hydroxy-8-iodo-2,2,5-trimethyl-3,4-dihydro-2H,1-benzopyran (14). Contrary to the earlier observations<sup>4,5</sup> it was not possible to effect the

deiodination of 14 by refluxing with N,N-dimethylaniline. Iodochroman (14) on Perkin condensation with acetic anhydride and sodium acetate gave 10-iodo-2,2,5-trimethyl-3,4-dihydro-2H,8H-benzo[1,2-*b*:5,4-*b'*]dipyrans-8-one (15), which on deiodination with Zn-HCl led to the formation of 16 (5-methyldihydroxanthyletin). Dehydrogenation of 16 with DDQ or NBS resulted in the required compound (11). Similarly 12 was obtained from 13 by Perkin condensation with acetic anhydride sodium phenylacetate. The formed 10-iodo compound (17) on treatment with Zn-HCl gave 2,2,5-trimethyl-7-phenyl-3,4-dihydro-2H,8H-benzo[1,2-*b*:5,4-*b'*]di-

pyran-8-one (18). Its dehydrogenation with DDQ or NBS gave the required xanthyletin (12).

The above method involving the formation of the coumarin ring on a preformed formylchroman appears convenient for the synthesis of 5-methylxanthyletin and seselin derivatives. The use of iodo group as the blocking agent constitutes a convenient route for the synthesis of linear pyranocoumarins.

### Experimental Procedure

Melting points are uncorrected. The PMR spectra were recorded in  $\text{CDCl}_3$  on a Perkin-Elmer R-32 instrument with TMS as an internal standard. Chemical shifts are given in  $\delta$  (ppm) values.

#### Reaction of $\beta$ -orcinaldehyde (1) with 2-methylbut-1,3-diene

A solution of isoprene (1.2 ml) in pet. ether (5 ml) was added to a mixture of  $\beta$ -orcinaldehyde (1 g, 6 mmol), orthophosphoric acid (85%, 2 ml) and pet. ether (5 ml) with constant stirring at 30–35°C during 4 hr. Stirring was continued for further 12 hr and then the mixture neutralized with aq. sodium bicarbonate (5%). It was extracted with ether, the ether extract washed with water, dried ( $\text{MgSO}_4$ ) and distilled. The residue thus obtained was found to be a mixture of three products (TLC). It was subjected to column chromatography and elution of the column with pet. ether gave the following three fractions successively.

#### Fraction A: 6-Formyl-7-hydroxy-2,2,5-trimethyl-3,4-dihydro-2H-1-benzopyran (4)

It crystallised from pet. ether as colourless shining crystals (0.05 g, 4%), m.p. 79–81° (Found: C, 71.0; H, 7.1.  $\text{C}_{13}\text{H}_{16}\text{O}_3$  requires C, 70.9; H, 7.3%); PMR: 1.30 [s, 6H,  $\text{C}(\text{CH}_3)_2$ ], 1.75 (t,  $J=7$  Hz, 2H, H-3), 2.15 (s, 3H,  $\text{CH}_3$ ), 2.55 (t,  $J=7$  Hz, 2H, H-4), 6.25 (s, 1H, H-8), 11.50 (s, 1H, CHO) and 13.50 (s, 1H, OH exchangeable with  $\text{D}_2\text{O}$ ).

#### Fraction B: 6-Formyl-5-hydroxy-2,2,7-trimethyl-3,4-dihydro-2H-1-benzopyran (3)

It crystallised from pet. ether as light yellow needles (0.45 g, 32%), m.p. 53–55° (Found: C, 70.8; H, 7.4.  $\text{C}_{13}\text{H}_{16}\text{O}_3$  requires C, 70.9; H, 7.3%); PMR: 1.35 [s, 6H,  $\text{C}(\text{CH}_3)_2$ ], 1.80 (t,  $J=7$  Hz, 2H, H-3), 2.45 (s, 3H,  $\text{CH}_3$ ), 2.60 (t,  $J=7$  Hz, 2H, H-4), 6.15 (s, 1H, H-8), 10.30 (s, 1H, CHO) and 13.00 (s, 1H, OH exchangeable with  $\text{D}_2\text{O}$ ).

#### Fraction C: 6-Formyl-2,2,5,8,8-pentamethyl-3,4,9,10-tetrahydro-2H,8H-benzo[1,2-b:3,4-b']dipyran (2)

It crystallized from pet. ether as white plates (0.4 g,

24%), m.p. 87–89° (Found: C, 74.2; H, 8.5.  $\text{C}_{18}\text{H}_{24}\text{O}_3$  requires C, 74.0; H, 8.7%); PMR: 1.30 [s, 12H,  $2 \times \text{C}(\text{CH}_3)_2$ ], 1.75 (m, 4H, H-3 and H-9), 2.45 (s, 3H,  $\text{CH}_3$ ), 2.55 (t,  $J=7$  Hz, 4H, H-4 & H-10) and 10.90 (s, 1H, CHO).

#### Conversion of 4 into 2

A solution of isoprene (0.05 ml) in pet. ether (2 ml) was added to a mixture of 4 (0.1 g, 0.4 mmol), orthophosphoric acid (85%, 0.2 ml) and pet. ether (2 ml) with constant stirring at 30–35°C during 4 hr. Stirring was continued for further 12 hr and the reaction was worked-up as above to yield 2 (0.06 g, 50%), m.p. and m.m.p. 87–89°.

#### 5,8,8-Trimethyl-2H,8H-benzo[1,2-b:3,4-b']dipyran-2-one (6) via 5,8,8-trimethyl-9,10-dihydro-2H,8H-benzo[1,2-b:3,4-b']dipyran-2-one

Monochroman (3, 1.0 g, 4 mmol), fused sodium acetate (2 g) and acetic anhydride (4 ml) were refluxed at 200–10°C for 12 hr. The excess anhydride was distilled under reduced pressure, contents cooled and poured onto crushed ice. The separated solid was filtered, washed with water and crystallized from benzene as colourless crystals of 5 (0.9 g, quantitative 100%), m.p. 123–25° (Found: C, 74.0; H, 6.4%.  $\text{C}_{15}\text{H}_{16}\text{O}_3$  requires C, 73.8; H, 6.6%); PMR: 1.35 [s, 6H,  $\text{C}(\text{CH}_3)_2$ ], 1.80 (t,  $J=7$  Hz, 2H, H-9), 2.35 (s, 3H,  $\text{CH}_3$ ), 2.85 (t,  $J=7$  Hz, 2H, H-10), 6.15 (d,  $J=9.5$  Hz, 1H, H-3), 6.50 (s, 1H, H-6) and 7.75 (d,  $J=9.5$  Hz, 1H, H-4).

The above chroman (5, 0.1 g, 0.4 mmol) was refluxed with DDQ (0.09 g) in anhydrous benzene (10 ml) for 72 hr. The solution was filtered, washed successively with sodium bicarbonate (10%), water, dried ( $\text{MgSO}_4$ ) and distilled. The residue thus obtained was crystallised from benzene-pet. ether to give light yellow crystals of 6 (0.07 g, 70%), m.p. 138–40° (Found: C, 74.0; H, 6.0.  $\text{C}_{15}\text{H}_{14}\text{O}_3$  requires C, 74.3; H, 5.8%); PMR: 1.50 [s, 6H,  $\text{C}(\text{CH}_3)_2$ ], 2.45 (s, 3H,  $\text{CH}_3$ ), 5.65 (d,  $J=9.5$  Hz, 1H, H-9), 6.15 (d,  $J=9$  Hz, 1H, H-3), 6.55 (s, 1H, H-6), 6.85 (d,  $J=9.5$  Hz, 1H, H-10) and 7.75 (d,  $J=9$  Hz, 1H, H-4).

Dehydrogenation of 5 by NBS in presence of benzoyl peroxide in anhydrous  $\text{CCl}_4$  also afforded 6.

#### Authentic 6: 5-Methyl-7-(1,1-dimethylprop-2-ynyloxy)-2H-1-benzopyran-2-one (8)

A solution of 7-hydroxy-5-methylcoumarin (1 g, 6 mmol) in dry acetone (100 ml) was refluxed with 3-chloro-3-methylbut-1-yne (2 ml) in the presence of anhydrous potassium carbonate (3 g) and potassium iodide (1.5 g) for 24 hr. Usual work-up yielded 8 (0.7 g, 50%) which crystallised from benzene as light yellow

crystals, m.p. 165-66° (Found: C, 74.2; H, 6.0.  $C_{15}H_{14}O_3$  requires C, 74.3; H, 5.8%); PMR: 1.75 [s, 6H,  $C(CH_3)_2$ ], 2.50 (s, 3H,  $CH_3$ ), 2.70 (s, 1H,  $C\equiv CH$ ), 6.25 (d,  $J=10$  Hz, 1H, H-3), 6.85 & 7.25 (d, each,  $J=2.5$  Hz, 1H each, H-6 & H-8) and 7.80 (d,  $J=10$  Hz, 1H, H-4).

The above coumarin (**8**, 0.5 g, 2 mmol) was refluxed in *N,N*-dimethylaniline (3 ml) for 12 hr. The cooled reaction mixture was poured into ice cold hydrochloric acid, extracted with ethyl acetate ( $3 \times 50$  ml), organic layer successively washed with 5% HCl, 5% NaOH, water and dried ( $MgSO_4$ ). Distillation of ethyl acetate yielded **6** which crystallised from benzene-pet. ether as light yellow crystals (0.2 g, 40%), m.p. and m.m.p. 138-40°.

5,8,8-Trimethyl-3-phenyl-2H,8H-benzo-[1,2-b:3,4-b']dipyran-2-one (**9**) via 5,8,8-Trimethyl-3-phenyl-1,9,10-dihydro-2H,8H-benzo[1,2-b:3,4-b']dipyran-2-one (**10**)

Formyl chroman (**3**, 1 g, 5 mmol), fused sodium phenyl acetate (2 g) and acetic anhydride (5 ml) were refluxed at 200-210°C for 12 hr. Usual work-up as in **5**, gave **10** which crystallised from benzene (0.9 g, 60%) m.p. 160-62° (Found: C, 78.5; H, 6.0.  $C_{21}H_{20}O_3$  requires C, 78.7; H, 6.2%); PMR: 1.35 [s, 6H,  $C(CH_3)_2$ ], 1.80 (t,  $J=7$  Hz, 2H, H-9), 2.40 (s, 3H,  $CH_3$ ), 2.85 (t,  $J=7$  Hz, 2H, H-10), 6.50 (s, 1H, H-6), 7.30 (m, 3H, H-3', H-4' and H-5'), 7.60 (m, 2H, H-2' and H-6') and 7.80 (s, 1H, H-4).

The above chroman (**10**, 0.1 g, 3 mmol) was refluxed with DDQ (0.07 g) in anhydrous benzene (10 ml). The reaction was worked-up as in case of **6** and the product crystallised from benzene-pet. ether to give yellow crystals of **9** (0.08 g, 80%), m.p. 182-84° (Found: C, 79.2; H, 5.8.  $C_{21}H_{18}O_3$  requires C, 79.0; H, 5.7%); PMR: 1.40 [s, 6H,  $C(CH_3)_2$ ], 2.40 (s, 3H,  $CH_3$ ), 5.60 (d,  $J=9.5$  Hz, 1H, H-9), 6.50 (s, 1H, H-6), 6.85 (d,  $J=9.5$  Hz, 1H, H-10), 7.30 (m, 3H, H-3', H-4' and H-5'), 7.60 (m, 2H, H-2' and H-6') and 7.80 (s, 1H, H-4).

Dehydrogenation of **10** with NBS, as in the case of **8** gave **9** in 70% yield.

2,4-Dihydroxy-3-iodo-6-methylbenzaldehyde (**13**)

$\beta$ -Orcinaldehyde (**1**, 2 g, 10 mmol) was dissolved in minimum amount of ethanol and to this solution iodine (0.72 g) and periodic acid (0.22 g in water) were added. The mixture was stirred for 2 hr at 60-70°C and diluted with water to give **13** (1.3 g, 50%) which crystallised from ethanol as white crystals, m.p. 192-94° (Found: C, 34.4; H, 2.7.  $C_{10}H_7O_3I$  requires C, 34.5; H, 2.5%); acetate ( $Ac_2O$  Py), m.p. 103-5° (Found: C, 40.0; H, 3.2.  $C_{12}H_9O_5I$  requires C, 39.8; H, 3.0%); PMR: 2.40 and 2.45 (each, 2  $\times$   $OCOCH_3$ ), 2.60 (s, 3H,  $CH_3$ ), 6.90 (s, 1H, H-5) and 9.80 (s, 1H, CHO).

6-Formyl-7-hydroxy-8-iodo-2,2,5-trimethyl-3,4-dihydro-2H-1-benzopyran (**14**)

A solution of isoprene (0.6 ml) in pet. ether (5 ml) was added to a mixture of **13** (1 g, 40 mmol), orthophosphoric acid (2 ml, 85%) and pet. ether (5 ml) with constant stirring at 30-35°C during 4 hr. Stirring was continued for further 12 hr and the reaction mixture worked-up as in case of **4**, and the product crystallised from benzene-pet. ether as shining colourless crystals of **14** (0.8 g, 50%), m.p. 185-87° (Found: C, 45.2; H, 4.5.  $C_{13}H_{15}O_3I$  requires C, 45.0; H, 4.3%); PMR: 1.35 [s, 6H,  $C(CH_3)_2$ ], 1.85 (t,  $J=7$  Hz, H-3); 2.40 (s, 3H,  $CH_3$ ); 2.60 (t,  $J=7$  Hz, 2H, H-4), 11.00 (s, 1H, CHO) and 13.40 (s, 1H, OH, exchangeable with  $D_2O$ ).

10-Iodo-2,2,5-trimethyl-3,4-dihydro-2H,8H-benzo-[1,2-b:5,4-b']dipyran-8-one (**15**)

**14** (0.5 g, 2 mmol) and fused sodium acetate (2 g) were refluxed with acetic anhydride (4 ml) at 200-10° for 12 hr. Usual work-up as in **5** afforded **15** which crystallised from benzene (0.2 g, 25%), m.p. 228-30° (Found: C, 50.0; H, 4.2.  $C_{15}H_{15}O_3I$  requires C, 48.7; H, 4.0%); PMR: 1.30 [s, 6H,  $C(CH_3)_2$ ], 1.80 (t,  $J=7$  Hz, 2H, H-3), 2.25 (s, 3H,  $CH_3$ ), 2.65 (t,  $J=7$  Hz, 2H, H-4), 6.10 (d,  $J=10$  Hz, 1H, H-7) and 7.75 (d,  $J=10$  Hz, 1H, H-6).

2,2,5-Trimethyl-3,4-dihydro-2H,8H-benzo-[1,2-b:5,4-b']dipyran-8-one (**16**)

A solution of (**15**, 0.5 g, 1 mmol) in ethyl alcohol (15 ml) was refluxed with zinc dust (0.2 g) and conc. hydrochloric acid (1.5 ml) for 4 hr. The solution was filtered, evaporated and the separated product crystallised from benzene-pet. ether as colourless plates (0.3 g, quantitative) of **16**, m.p. 164-65° (Found: C, 74.0; H, 6.8.  $C_{15}H_{16}O_3$  requires C, 73.8; H, 6.6%); PMR: 1.35 [s, 6H,  $C(CH_3)_2$ ], 1.80 (t,  $J=7$  Hz, 2H, H-3), 2.35 (s, 3H,  $CH_3$ ), 2.70 (t,  $J=7$  Hz, 2H, H-4), 6.15 (d,  $J=9$  Hz, 1H, H-7), 6.60 (s, 1H, CHO) and 7.80 (d,  $J=9$  Hz, 1H, H-6).

2,2,5-Trimethyl-2H,8H-benzo[1,2-b:5,4-b']dipyran-8-one (**11**)

The above chroman (**16**, 0.1 g, 0.4 mmol) was refluxed with DDQ (0.09 g) in anhydrous benzene (10 ml) for 72 hr. The reaction was worked-up as in case of **6**. It crystallised from benzene-pet. ether to give colourless shining crystals of **11** (0.07 g, 70%), m.p. 148-50° (Found: C, 74.5; H, 6.0.  $C_{15}H_{14}O_3$  requires C, 74.3; H, 5.8%); PMR: 1.50 [s, 6H,  $C(CH_3)_2$ ], 2.40 (s, 3H,  $CH_3$ ), 5.70 (d,  $J=9.5$  Hz, 1H, H-3), 6.20 (d,  $J=9$  Hz, 1H, H-7), 6.55 (d,  $J=9.5$  Hz, 1H, H-4), 6.60 (s, 1H, H-10) and 7.80 (d,  $J=9$  Hz, 1H, H-6).

**10-Iodo-2,2,5-trimethyl-7-phenyl-3,4-dihydro-2H,8H-benzo[1,2-b:5,4-b']dipyran-8-one (17)**

A mixture of **14** (0.5 g, 2 mmol), fused sodium phenyl acetate (2 g) and acetic anhydride (4 ml) was refluxed at 200–10°C for 12 hr. The reaction mixture was worked-up as in the case of **10**. Product crystallised from benzene to give **17** (0.3 g, 35%), m.p. 235–40° (Found: C, 56.8; H, 4.5.  $C_{21}H_{19}O_3I$  requires C, 56.6; H, 4.3%); PMR: 1.40 (s, 6H,  $C(CH_3)_2$ ), 1.85 (t,  $J=7$  Hz, 2H, H-3), 2.40 (s, 3H,  $CH_3$ ), 2.75 (t,  $J=7$  Hz, 2H, H-4), 7.35 (m, 3H, H-3', H-4' & H-5'), 7.65 (m, 2H, H-2' & H-6') and 7.90 (s, 1H, H-6).

**2,2,5-Trimethyl-7-phenyl-3,4-dihydro-2H,8H-benzo[1,2-b:5,4-b']dipyran-8-one (18)**

**17** (0.5 g, 1 mmol) in ethyl alcohol (15 ml) was refluxed with zinc dust (0.2 g) and conc. hydrochloric acid (1.5 ml) for 4 hr. The solution was filtered, evaporated and the separated product crystallised from benzene-pet. ether as light yellow crystals of **18** (0.3 g, 90%), m.p. 155–56° (Found: C, 79.0; H, 6.3.  $C_{21}H_{20}O_3$  requires C, 78.7; H, 6.2%); PMR: 1.35 [s, 6H,  $C(CH_3)_2$ ], 1.85 (t,  $J=7$  Hz, 2H, H-3), 2.35 (s, 3H,  $CH_3$ ), 2.70 (t,  $J=7.0$  Hz, 2H, H-4), 6.65 (s, 1H, H-10), 7.35 (m, 3H, H-3', H-4' and H-5'), 7.65 (m, 2H, H-2' & H-6') and 7.95 (s, 1H, H-6).

**2,2,5-Trimethyl-7-phenyl-2H,8H-benzo[1,2-b:5,4-b']dipyran-8-one (12)**

The above chroman (**18**, 0.1 g, 0.3 mmol) was refluxed with DDQ (0.07 g) in anhydrous benzene (10 ml) for 72 hr. The reaction mixture was worked-up

as in case of **11**. The residue, thus obtained, was crystallised from benzene-pet. ether to give colourless shining crystals of **12** (0.08 g, 80%), m.p. 175–76° (Found: C, 79.2; H, 5.8.  $C_{21}H_{18}O_3$  requires C, 79.0; H, 5.7%); PMR: 1.45 [s, 6H,  $C(CH_3)_2$ ], 2.40 (s, 3H,  $CH_3$ ), 5.60 (d,  $J=10$  Hz, 1H, H-3), 6.50 (s, 1H, H-10), 6.85 (d,  $J=10$  Hz, 1H, H-4), 7.30 (m, 3H, H-3', H-4' and H-5'), 7.60 (m, 2H, H-2', H-6') and 7.80 (s, 1H, H-6).

Dehydrogenation of **18** with NBS also afforded **12**.

**Acknowledgements**

Our thanks are due to CSIR, New Delhi for financial assistance.

**References**

- 1 Ollis W D, Sutherland I O, *Isoprenoid units in natural phenolic compounds, Chapter in chemistry of natural phenolic compounds*, edited by W D Ollis (Pergamon Press, London), 1961, 74.
- 2 Cardillo G, Cricchio R & Merlini L, *Tetrahedron*, **24** (1968) 4825.
- 3 Majumdar A S & Usgaonkar R N, *Indian J chem*, **10** (1972) 672.
- 4 Bell J C, Robertson A & Subramaniam T S, *J chem Soc*, (1936) 627.
- 5 Robertson A & Subramaniam T S, *J chem Soc* (1937) 286.
- 6 Bell J C, Bridge W, Robertson A & Subramaniam T S, *J chem Soc*, (1937) 1542.
- 7 Dean F M, *Naturally occurring oxygen ring compounds* (Butterworth, London), 1963, 198.
- 8 Chakraborty A, Das Gupta A & Bose P K, *Ann Biochem exp Med*, **17** (1957) 50.
- 9 Joshi B S, Viswanathan N, Kaul C L & Grewal P S, *Indian J Chem*, **19B** (1980) 495.
- 10 Ahluwalia V K, Prakash Chandra & Singh R P, *Tetrahedron*, **35** (1970) 2081.
- 11 Shah M B & Sethna V M, *J chem Soc*, (1959) 2676.

## Synthesis of Bicyclic Oxygen Heterocycles: Part II—Synthesis of 9-Aryloxy-3-bromo-2,4-ethanochromans

S CHATTOPADHYAY, B K SEN & K C MAJUMDAR\*

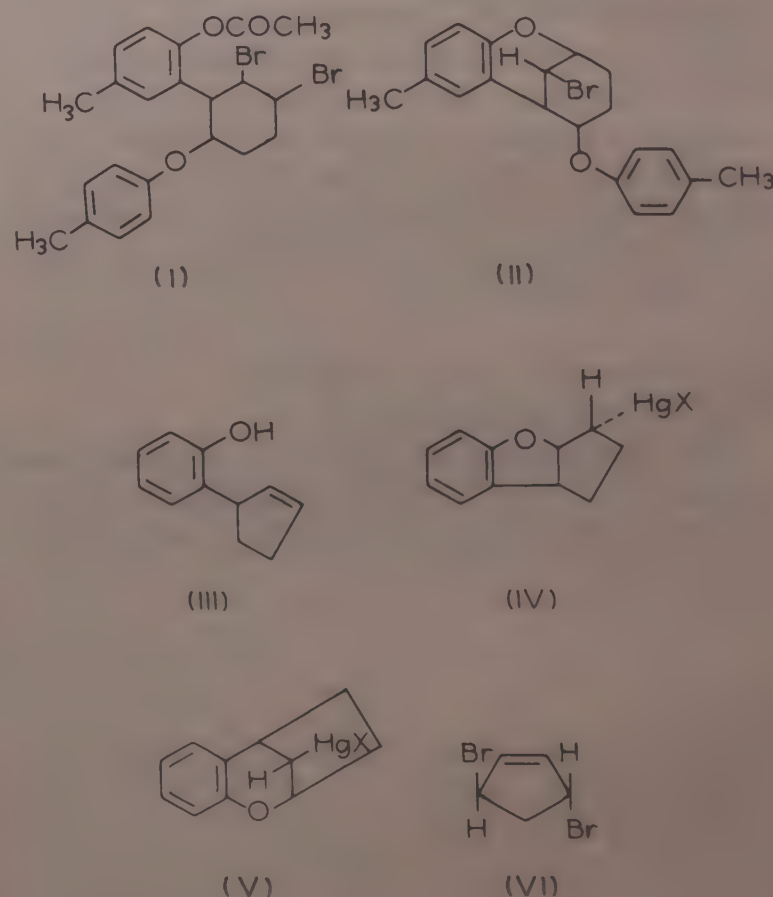
Department of Chemistry, University of Kalyani, Kalyani 741 235

Received 25 February 1985; accepted 10 May 1985

Thermal [3,3] sigmatropic shift of 3,5-diaryloxycyclopentenes (VII) give 2-(5'-aryloxy-2'-cyclopentenyl)phenols (VIII) as viscous oils which on treatment with acetic anhydride and pyridine furnish the corresponding acetyl derivatives (IX). The latter compounds consume one mol of bromine and the acetyl dibromo derivatives (X) thus obtained undergo base-catalysed cyclisation to give the title compounds (XII). Chloromercuration of VIIIa (R = CH<sub>3</sub>) gives 3-chloromercuri-1-(*p*-cresoxy)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (XIa) via internal nucleophilic attack at C-2 of the cyclopentenyl ring.

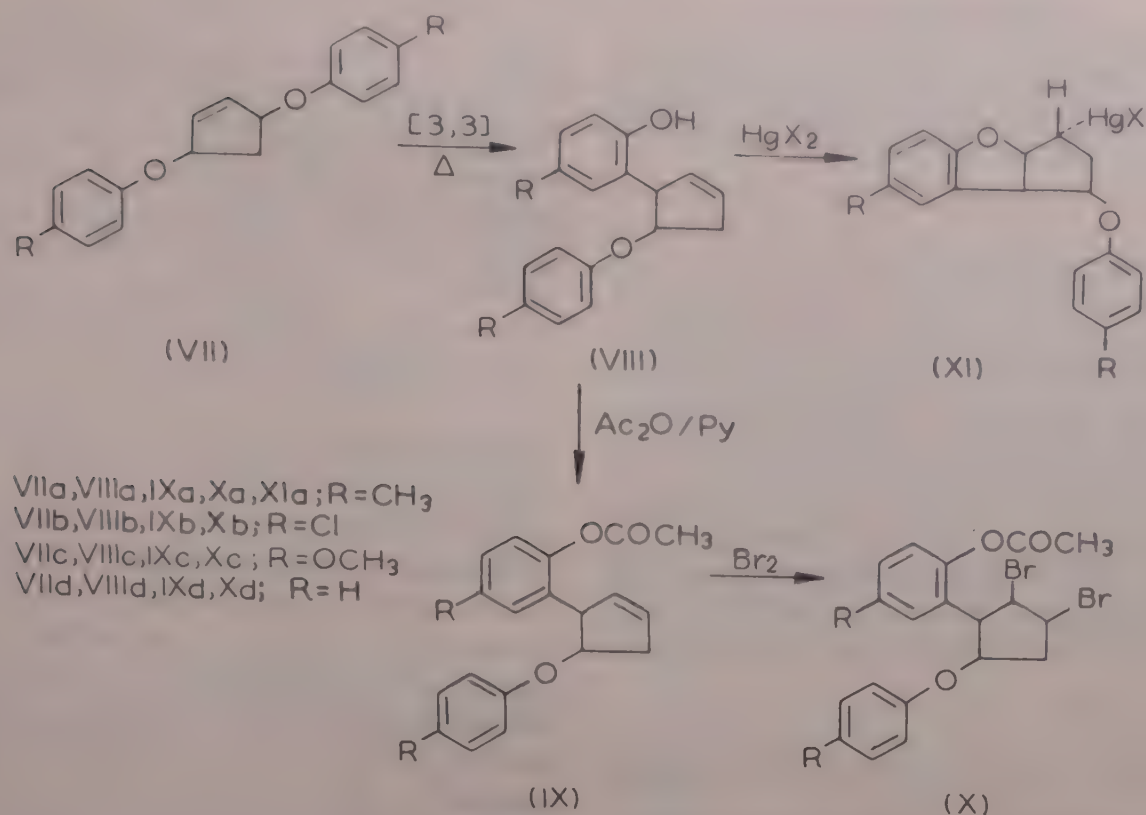
The ring closure reaction of the dibromo derivative (I) of 2-[6'-(*p*-cresoxy)-2'-cyclohexenyl]-4-methylphenol acetate which we have recently studied<sup>1</sup> gives 3-bromo-9-(*p*-cresoxy)-6-methyl-2,4-propanochroman (II). The same pathway is also followed during PhSeCl<sup>2</sup> and HgCl<sub>2</sub> induced reaction of 2-(2'-cyclohexenyl)phenol to give bicyclic products. In contrast to the above observations it has been found that the PhSeCl and HgX<sub>2</sub> (X = -Cl, -OAc) induced cyclisation of 2-(2'-cyclopentenyl)phenol (III) gives the 3-substituted tetrahydro-1*H*-cyclopenta[*b*]benzofuran (IV) and no bicyclic product of the type V. These confornting reports prompted us to prepare the dibromo derivatives of 2-(5'-aryloxy-2'-cyclopentenyl)phenol acetates and study their base-catalysed cyclisation to ascertain whether the internal nucleophylic attack occurs at C-2 carbon<sup>4-6</sup> or at C-3 carbon<sup>1</sup> of the allylic side chain.

The starting material 3,5-dibromocyclopentene (VI) was prepared by the allylic bromination of cyclopentene with N-bromosuccinimide in refluxing carbon tetrachloride (78°/2 hr). This compound was prepared earlier by the 1,4-addition of bromine to cyclopentadiene<sup>7</sup> and its stereochemistry established through chemical transformation and dipole moment measurement<sup>8</sup>. The *cis*-isomer (an unstable solid, m.p. 45°, b.p. 72-75°/2 mm) was prepared at -35° which during distillation got converted into the thermodynamically stable *trans*-isomer. Thus, the method of preparation and the recorded b.p. indicates the compound at our hand to be the *trans*-isomer. The *trans*-3,5-diaryloxycyclopentenes (VII) were prepared by S<sub>N</sub>2 displacement of *trans*-3,5-dibromocyclopentene (VI) with appropriate phenoxides. The 2-(5'-aryloxy-2'-cyclopentenyl)phenols (VIII) were obtained as viscous oils by the thermal *ortho*-Claisen rearrangement of VII. These phenols (VIII) responded positively to ferric

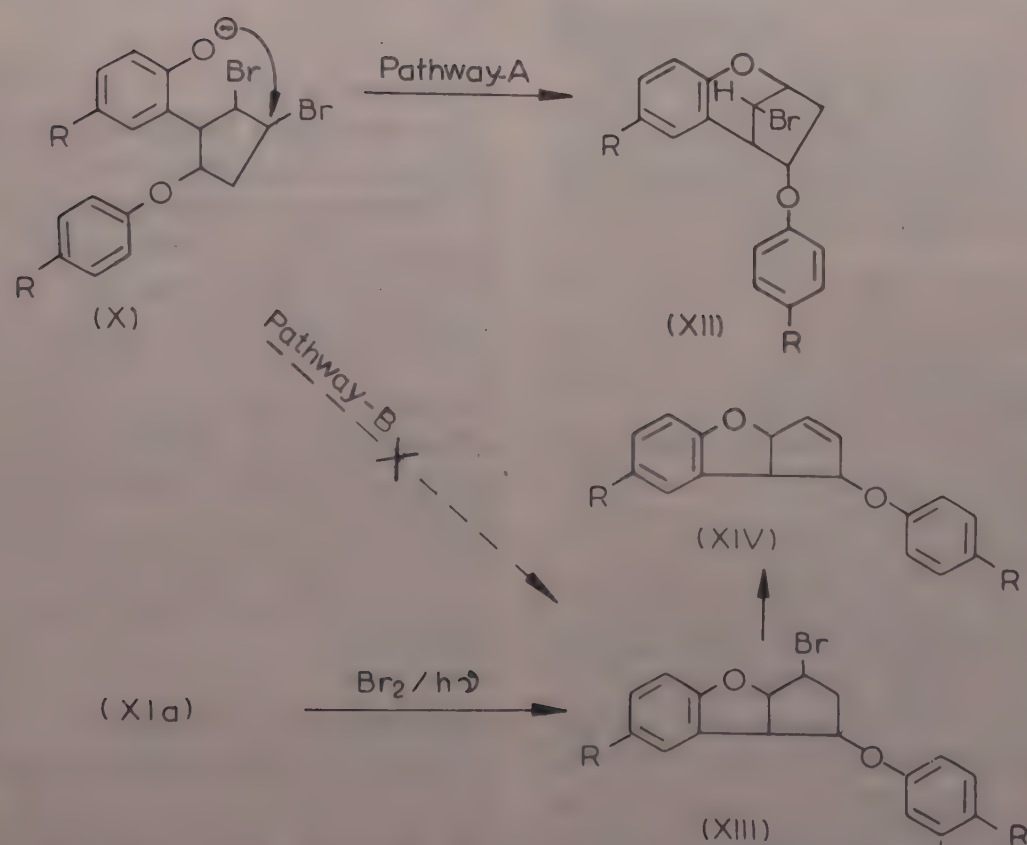


chloride reaction and were converted into solid acetyl derivatives (IX) which added one mol of bromine to give the corresponding dibromo derivatives (X). 2-[5'-(*p*-Cresoxy)-2'-cyclopentenyl]-4-methylphenol (VIIIa) in ethanol when treated with mercuric chloride solution gave 3-chloromercuri-1-(*p*-Cresoxy)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (XIa) by the internal nucleophylic attack at C-2 carbon of the cyclopentenyl side chain (Scheme 1).

The dibromo acetate derivative (X) when treated with ethanolic potassium hydroxide afforded the title compounds 9-aryloxy-3-bromo-2,4-ethanochromans (XII) which were resistant to dehydrobromination with



Scheme 1



XIIa, XIIIa, XIVa; R = CH<sub>3</sub>  
 XIIb, R = Cl; XIIc, R = OCH<sub>3</sub>;  
 XIId, R = H

Scheme-2

sodium ethoxide in ethanol or potassium *t*-butoxide in *t*-butanol under reflux. The mercurated product (XI) on treatment with bromine in sunlight underwent replacement of the chloromercuri group by a bromine atom giving the compound XIII. This compound was dehydrobrominated with ethanolic potassium hy-

dride to the compound XIV which could have been obtained from X directly if pathway-B were followed (Scheme 2).

#### Experimental Procedure

Melting points are uncorrected. 90 MHz PMR

spectra were recorded on a Varian instrument using carbon tetrachloride or chloroform- $d_1$  as solvent and TMS as internal standard (chemical shifts in  $\delta$ , ppm) and IR spectra in KBr on a Perkin-Elmer model 237B ( $\nu_{max}$  in  $\text{cm}^{-1}$ ).

#### *trans*-3,5-Dibromocyclopentene (VI)

To a solution of NBS (0.2 mol, 35.6 g) in dry  $\text{CCl}_4$  (200 ml) under reflux, cyclopentene (0.1 mol, 6.8 g) in dry  $\text{CCl}_4$  (25 ml) was added dropwise during 20 min. and the refluxing continued for 1 hr. After cooling, the insoluble succinimide was filtered off and washed with  $\text{CCl}_4$ . The filtrate was washed with a freshly prepared saturated solution of aq.  $\text{NaHSO}_3$  followed by water and dried over anhyd.  $\text{Na}_2\text{SO}_4$ . Removal of solvent gave the product as a viscous liquid, yield 25% (5.1 g), b.p.  $54-55^\circ/2$  mm. It was used as such in the subsequent step.

#### *trans*-3,5-Bis-aryloxy-cyclopentenenes (VII): General procedure

A mixture of appropriate phenol (0.1 mol) and KOH (0.1 mol) in 90% ethanol (150 ml) was refluxed for 1 hr, cooled and compound VI (0.05 mol) added to it with stirring. The reaction mixture was further stirred for 6 hr. The resultant KBr was filtered off, solvent removed *in vacuo* and the residue poured into water. The solid formed was filtered, washed thoroughly with water and dried. Following compounds were thus prepared:

VIIa: m.p.  $85^\circ$ , yield 50% (Found: C, 81.3; H, 7.1.  $\text{C}_{19}\text{H}_{20}\text{O}_2$  requires C, 81.4; H, 7.1%).

VIIb: m.p.  $102^\circ$ , yield 60% (Found: C, 63.1; H, 4.5.  $\text{C}_{17}\text{H}_{14}\text{O}_2\text{Cl}_2$  requires C, 63.6; H, 4.4%).

VIIc: m.p.  $90^\circ$ , yield 65% (Found: C, 73.0; H, 6.5.  $\text{C}_{19}\text{H}_{20}\text{O}_4$  requires C, 73.1; H, 6.4%).

VIIId: m.p.  $78^\circ$ , yield 55% (Found: C, 81.1; H, 6.3.  $\text{C}_{17}\text{H}_{16}\text{O}_2$  requires C, 81.0; H, 6.4%).

The IR spectra of VII showed the presence of an olefinic double bond (820) and an ether function (1200-1250). Their PMR ( $\text{CDCl}_3$ , 90 MHz) data are as follows—VIIa: 2.25 (s, 6H), 2.85-3.20 (m, 2H), 5.10-5.27 (m, 2H), 6.26 (s, 2H), 6.80-7.25 (q, 8H); VIIb: 2.80-3.20 (m, 2H), 5.00-5.25 (m, 2H), 6.20 (s, 2H), 6.70-7.30 (m, 8H); VIIc: 2.8-3.0 (m, 2H), 5.00-5.40 (m, 2H), 6.10-6.25 (m, 2H), 6.70-6.90 (m, 8H), 3.75 (s, 6H); VIIId: 2.80-3.20 (m, 2H), 5.20-5.40 (m, 2H), 6.3-6.4 (m, 2H), 6.8-7.5 (m, 10H).

#### Rearrangement of VII: General procedure

Compound VII (2 g) was refluxed in *N,N*-diethylaniline (12 ml) for 10 hr. and the reaction mixture concentrated under reduced pressure ( $18/0.1$  mm) to remove most of diethylaniline. The residual mass was poured into ice-cold dil. HCl (1:1),

extracted with ether, washed with saturated solution of NaCl and dried ( $\text{Na}_2\text{SO}_4$ ). The highly viscous liquid obtained after removal of ether was purified by passing through a silica gel column and eluting with pet. ether-benzene (2:1). The product thus obtained was a viscous oil, yield (VIIa) 1.25 g (62%), (VIIb) 1.1 g (55%), (VIIc) 1.4 g (70%), (VIIId) 1 g (50%). The IR spectrum of 2-[5'-(*p*-cresoxy)-2'-cyclopentenyl]-*p*-cresol (VIIa) exhibited bands at 3400 ( $-\text{OH}$ ), 1200 ( $\text{C}-\text{O}-\text{C}$ ) and 800 ( $-\text{C}=\text{C}-$ ).

#### Chloromercuration of 2-[5'-(*p*-cresoxy)-2'-cyclopentenyl]-*p*-cresol (VIIa)

To a solution of  $\text{HgCl}_2$  (0.52 g, 2 mmol) in water (10 ml) under stirring was added VIIa (0.5 g, 2 mmol) and stirring continued for 24 hr at room temperature during which a greyish oil settled down. The aqueous layer was decanted off and a few drops of methanol were added to the oil. The resulting white precipitate was filtered, dried and recrystallised from chloroform-methanol to give XIa, yield 65% (0.51 g), m.p.  $195^\circ$ ; PMR: 1.45-1.90 (m, 2H), 2.25 (s, 6H), 3.10 (m, 1H), 3.8-4.1 (m, 1H), 4.6-5.0 (m, 1H), 5.4-5.6 (m, 1H), 6.4-7.2 (m, 7H).

#### Bromination of XIa

The mercurated product (XIa; 0.4 g) was taken in chloroform (20 ml) and warmed to  $50^\circ$ . The solution was then exposed to direct sunlight and a solution of bromine (2 drops) in  $\text{CHCl}_3$  (10 ml) added to it with stirring. After the bromine was used up, the mixture was stirred further for 45 min, and cooled in an ice-salt bath for 15 min. The precipitated mercuric bromide was filtered off, and the solution successively washed with saturated aq.  $\text{NaHSO}_3$  and salt water, dried ( $\text{Na}_2\text{SO}_4$ ) and solvent removed to give a highly viscous liquid which was purified by passing through silica gel column eluting with pet. ether-benzene (4:1). The product (XIII) thus obtained was a viscous liquid, yield 0.22 g (80%).

#### Dehydrobromination of XIII

Compound XIII was refluxed with ethanolic KOH for 4 hr, ethanol removed and the residue extracted with ether. The ether extract was washed repeatedly with salt-water and finally dried ( $\text{Na}_2\text{SO}_4$ ). Removal of solvent gave a white solid (XIV) which was recrystallised from chloroform-methanol, m.p.  $140^\circ$ , yield 90%; PMR: 2.25 (s, 6H), 3.95-4.15 (m, 1H), 5.1-5.3 (m, 1H), 5.7-5.9 (m, 1H), 6.1-6.25 (m, 2H), 6.5-7.4 (m, 7H).

#### Acetate derivatives (IXa-d)

The phenolic product VIIa (1.0 g) was taken in a mixture of dry pyridine (5 ml) and acetic anhydride

overnight. The mixture was then poured into crushed ice and scratched with a glass rod. It was extracted with ether, the ether extract washed successively with dil. HCl and salt water, dried ( $\text{Na}_2\text{SO}_4$ ) and solvent removed. The solid thus obtained was crystallised from dry ethanol to give IX. The characterization data of IXa-d, thus prepared, are as follows:

IXa: m.p.  $87^\circ$ ; IR: 1740 ( $-\text{OCOCH}_3$ ), 805 ( $-\text{C}=\text{C}-$ ) and 1200-1225 ( $-\text{C}-\text{O}-\text{C}-$ ); PMR: 2.2 (s, 6H), 2.3 (s, 3H), 2.70-2.85 (m, 2H), 4.20-4.35 (m, 1H), 5.0-5.2 (m, 1H), 5.85-6.15 (m, 2H), 6.6-7.3 (m, 7H); MS:  $m/z$  322 ( $\text{M}^+$ ) (Found: C, 78.10; H, 6.90.  $\text{C}_{21}\text{H}_{22}\text{O}_3$  requires C, 78.26; H, 6.83 %).

IXb: m.p.  $95^\circ$ .

IXc: Viscous liquid.

IXd: m.p.  $75^\circ$ ; PMR: 2.2 (s, 3H), 2.7-2.8 (m, 2H), 4.20-4.35 (m, 1H), 5.10-5.25 (m, 1H), 5.85-6.20 (m, 2H), 6.90-7.45 (m, 9H).

#### Bromination of acetate derivatives (IXa-d)

To a cold solution ( $0-5^\circ$ ) of IXa (1.5 g) in dry  $\text{CCl}_4$  (10 ml) was added a solution of bromine (0.4 g) in dry  $\text{CCl}_4$  (5 ml) dropwise for a period of 20 min and stirring continued for 4 hr at  $5-10^\circ$ . Thereafter, the reaction mixture was washed successively with a saturated solution of  $\text{NaHSO}_3$  and salt-water, dried ( $\text{Na}_2\text{SO}_4$ ), and solvent removed to give a highly viscous oil which on purification by column chromatography over silica gel using pet. ether ( $60-80^\circ$ ) as eluent gave Xa, as a sticky mass, yield 90%; PMR: 2.25 (s, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 2.7-2.8 (m, 2H), 4.0-4.1 (s, 1H), 4.15-4.25 (s, 1H), 4.6-4.9 (m, 1H), 6.75-7.25 (m, 7H).

Compounds Xb-d, obtained as sticky mass (yield 90-95 %), were prepared in a similar way and were used as such in the subsequent step.

#### Cyclisation of X: Formation of XII

To a solution of KOH (1 g) in dry ethanol (10 ml) was added a solution of Xa (0.7 g) in ethanol slowly with stirring. The mixture was then refluxed on a water-bath for 4 hr, left overnight, concentrated, extracted with

ether and the ether extract washed with saturated salt-water and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of solvent gave a red viscous oil which after column chromatography over silica gel and using pet. ether ( $60-80^\circ$ ) as eluent gave XIIa, m.p.  $152^\circ$ , yield 70 % (0.35 g); PMR: 2.15 (s, 3H), 2.35 (s, 3H), 2.4-2.7 (m, 2H), 4.1-4.3 (m, 2H), 4.6-4.9 (m, 1H), 5.1-5.3 (m, 1H), 6.75-7.30 (m, 7H) (Found: C, 63.3; H, 5.3.  $\text{C}_{19}\text{H}_{19}\text{O}_2\text{Br}$  requires C, 63.5; H, 5.3 %); MS:  $m/z$  358, 360 ( $\text{M}^+$ ).

Compounds XIIb-d were also prepared in a similar way. Their characterization data are as follows:

XIIb: m.p.  $148^\circ$ , yield 62%; PMR (400 MHz): 2.10-2.25 (m, 1H), 2.6-2.7 (m, 1H), 4.18-4.30 (m, 2H), 4.75-4.80 (m, 1H), 5.20-5.28 (m, 1H), 6.8-7.4 (m, 7H) (Found: C, 51.2; H, 3.1.  $\text{C}_{17}\text{H}_{13}\text{O}_2\text{Cl}_2\text{Br}$  requires C, 51.0; H, 3.3 %).

XIIc: m.p.  $100^\circ$ , yield 65%; PMR: 2.0-2.75 (m, 2H), 3.85 (s, 6H), 3.90-4.15 (m, 1H), 4.55-4.85 (m, 2H), 5.2-5.4 (m, 1H), 6.8-7.6 (m, 7H).

XIId: m.p.  $110^\circ$ , yield 55%; PMR: 2.00-2.8 (m, 2H), 3.35-3.55 (broad d, 1H), 4.6-4.9 (m, 3H), 6.7-7.4 (m, 9H).

#### Acknowledgement

The authors thank Prof J W Lown, Department of Chemistry, University of Alberta for the 400 MHz PMR spectrum of compound XIIb, Dr N C Ganguly of this department for helpful discussion and the University of Kalyani for financial assistance given to one of them (S C).

#### References

- 1 Sen B K & Majumdar K C, *Indian J Chem*, **22B** (1983) 1184.
- 2 Clive D J, Chittatu G, Curtis N J, Kiel W A & Wong C K, *Chem Commun*, (1977) 725.
- 3 Hosokawa T, Miyagi S, Murahashi S, Sonoda A, Matsuura Y, Tanimoto S & Kakudo M, *J org Chem*, **43** (1978) 719.
- 4 Gaertner R, *J Am chem Soc*, **73** (1951) 4400.
- 5 Thyagarajan B S, Balasubramanian K K & Bhima Rao R, *Tetrahedron*, **23** (1967) 3206.
- 6 Thyagarajan B S, Balasubramanian K K & Bhima Rao R, *Tetrahedron*, **23** (1967) 3533.
- 7 Blomquist A T & Meyer W G, *J org Chem*, **10** (1945) 134.
- 8 Young W G, Hal H K & Winstein S, *J Am chem Soc*, **78** (1956) 4338.

# Chemistry of Carbenes: Part III—Reaction of Methylene with Ethyl *n*-Propyl Ether

R K S MEHTA†

University of Edinburgh, Edinburgh, Scotland

Received 13 August 1984; revised 10 October 1984; accepted 16 May 1985

The bond reactivities for ethyl *n*-propyl ether, based on unity for the primary bonds of ethyl group, again prove the discriminate attack of methylene. All secondary bonds are attacked faster than the primary bonds of ethyl, the  $\beta$  C-H of ethyl itself being attacked 1.83 times, which is higher than the attack on secondary  $\alpha$  C-H (1.74) and  $\beta$  C-H (1.29) bonds. The descending order of reactivities of C-H bonds in propyl is  $\alpha > \beta > \gamma$ . Additional evidence of the electrophilic effect of ethereal oxygen on the insertion reactions as also on the displacement reaction where methylene gives a methyl alkyl ether and displaces an olefin has been obtained. Similarly, the predicted formation of aldehydes resulting from the abstraction reactions of methylene has been observed. These results obtained in gas phase contrasted with the liquid phase work of Doering *et al* [*J Am chem Soc*, 78(1956) 3224] who found the attack to be indiscriminate. This work further confirms the difference between the two phases.

The chemistry of carbenes along with the reaction of methylene with symmetrical ethers such as dimethyl and diethyl ether has been discussed earlier<sup>1,2</sup>. In order to understand the effect of asymmetry of a molecule on the relative rate of attack of methylene, ethyl *n*-propyl ether has now been selected for the study of reactivity of  $\alpha$ ,  $\beta$  and  $\gamma$  C-H bonds in the propyl group as compared to  $\alpha$  and  $\beta$  C-H bonds of ethyl group. It was also of interest to find how far the proximity of oxygen of ether influences the insertion reaction into a given C-H bond.

## Materials and Methods

The apparatus and procedure for the study of methylene biradicals has been described before<sup>3</sup>. Mixtures of ketene and ether in the ratios 1:1, 1:2, 1:3, keeping total pressure below 15 cm, were irradiated to about 20% decomposition of ketene. The relative rate of attack of methylene was studied at 20° and 100°C.

## Results and Discussion

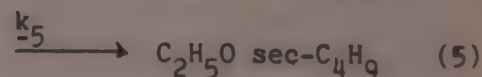
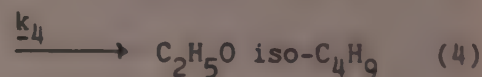
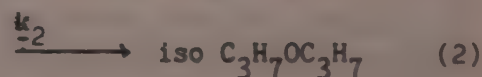
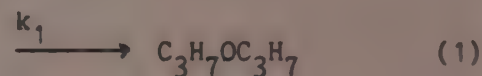
The gas chromatographic analysis showed the formation of about fifteen products, some of these arising as a result of insertion, displacement and abstraction reactions.

In steps (8) and (9) the methyl and ethyl radicals may further abstract hydrogen or dimerise, etc.

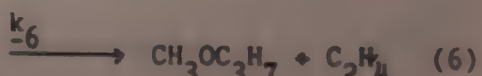
### Insertion reactions

The insertion of methylene into various C-H bonds of ethyl *n*-propyl ether gave rise to the products such as di-*n*-propyl ether (b.p. 90.5°), *n*-propyl isopropyl

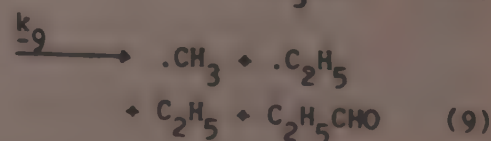
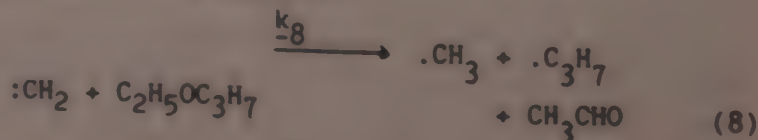
### (1) Insertion reactions:



### (2) Displacement reaction:

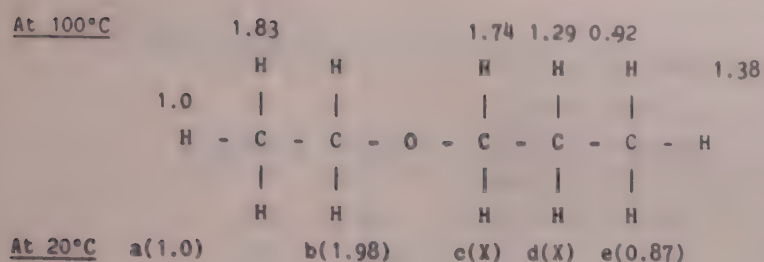


### (3) Abstraction reaction:



ether (83°), ethyl *s*-butyl ether (81.4°), ethyl isobutyl ether (81.1°) and ethyl *n*-butyl ether (92.3°) by the attack of methylene on bonds *a*, *b*, *c*, *d* and *e* of ethyl *n*-propyl ether respectively (see Scheme I).

†Present address: Polymers Department, General Motors Research Laboratories, Warren, Michigan 48090-9055 (USA)



Scheme 1

All the five ethers have been detected and the relative rates of attack of bonds are also shown in Scheme 1. Due to the close boiling points of ethyl *s*-butyl and ethyl isobutyl ethers, i.e. the insertion products at bonds *c* and *d* at 20°C, could not be separated, though at 100°C the molar ratios of products obtained via insertions *c/a*, *d/a* have been estimated to be 1.16 and 0.86, respectively. In view of small change for attack at *b* from 20°C to 100°C, attacks at *c* and *d* are unlikely to be much different from values at 100°C. Their peak areas were estimated by drawing a vertical division between them and were inevitably somewhat in error. They are reported as the combined area in Table 1.

It was possible, however, to separate  $\text{Pr}^i\text{OPr}^n$  from  $\text{EtOBu}^s$  where a reasonable estimate could be derived for the attack at *b/a* and *c/a* bonds. At 100°C, the molar ratio for the former was 1.22 and for the latter it was 1.16 (Table 1) each for two  $\beta$  C-H bonds compared to three  $\alpha$  ones. A correction factor of 3/2, therefore, gives ratios 1.83 and 1.74, respectively which show preference of attack on an  $\alpha$  C-H bond. For  $\beta$  CH bond, the molar ratio for the product  $\text{EtOBu}^i$  was 0.86 and comes to  $(0.86 \times 3/2)$  1.29 per bond. Thus, we have a descending order of reactivities  $1.74 > 1.29 > 0.92$  with C-H bonds on  $\alpha$ -,  $\beta$ -, and  $\gamma$ -carbon atoms in propyl group of ether. For  $\text{EtOBu}^n$ , where three  $\beta$  C-H bonds of propyl group compete with the corresponding three on ethyl side of the ether molecule, molar ratios 0.87 for 20°C and 0.92 for 100°C again indicate small preference of attack on the ethyl side. If one considers the preference of attack at the  $\alpha$  C-H bond in MeOMe which is 1.72 compared to 1.00 in

EtOEt to 0.92 for that on the propyl side in  $\text{EtOPr}^n$ , the influence of the oxygen of ether on such insertions may be substantiated. Thus, closer the primary bonds are to the oxygen atom, higher is the rate of insertion reaction.

#### Displacement reaction

Methylene has been found to undergo a displacement reaction with  $\text{EtOPr}^n$  to yield two sets of products. From reaction (6) methyl propyl ether and ethylene are formed and from (7) methyl ethyl ether and propylene are produced. Quantitative measurements of the lower ethers produced were carried out at two temperatures only. The molar ratio  $\text{MeOEt}/\text{Pr}^n\text{OPr}^n$  at 20°C was found to be 0.20, while at 100°C, it was 0.24. Similarly the molar ratio  $\text{MeOPr}^n/\text{Pr}^n\text{OPr}^n$  at 20°C was 0.30 which rose to 0.37 at 100°C (Tables 1 and 2). These reactions again seem to have low activation energies.

#### Abstraction reaction

It being known from the studies of diethyl ether that methylene abstracts secondary hydrogen to yield acetaldehyde<sup>1</sup>, the same reaction gave acetaldehyde from attack on ethyl side of  $\text{EtOPr}^n$ . The H-abstraction from  $\beta$  C-H bonds in propyl side yielded propionaldehyde as shown in step (9). The relative rates of formation of both the aldehydes have been measured and are given in Tables 1 and 2. At 100°C, the relative yields were considerably higher but were irreproducible. Only at room temperature (Table 2) could any reliable estimate of their relative rates of formation be obtained. At 20°C the molar ratios for acetaldehyde and propionaldehyde were found to be identical, viz. 0.5.

#### Bond reactivity of ethyl propyl ether

The data on insertion reaction products, given in Table 3, show that secondary bonds are attacked faster than the primary bonds of ethyl, and the secondary bond of ethyl of this ether is attacked 1.83 times faster at 20°C. This rate is a little higher than the rates of

Table 1—GLC Peak Areas of Products of Reactions of Methylene with Ethyl *n*-Propyl Ether at 100°C  
[Peak areas normalized to di-*n*-propyl ether]

	MeOEt	C <sub>2</sub> H <sub>5</sub> CHO	MeOPr <sup>n</sup>	EtOBu <sup>i</sup>	EtOBu <sup>s</sup>	Pr <sup>i</sup> OPr <sup>n</sup>	EtOBu <sup>n</sup>
	0.09	0.11	0.38	Impure	1.45	—	—
	0.09	0.19	0.28	Impure	1.45	1.21	1.20
	0.11	0.25	0.21	Impure	—	1.20	1.20
	0.10	0.64	0.24	Impure	—	1.12	1.29
	0.14	0.66	0.44	1.19	1.40	1.06	1.30
	0.21	0.23	(0.21)	1.08	1.28	—	1.15
Av:	0.12	Varies	0.31	1.14	1.40	1.15	1.23
Av molar ratio:	0.24	—	0.37	0.86	1.16	1.22	0.92

Table 2—GLC Peak Areas of Products of Reactions of Methylene with Ethyl *n*-Propyl Ether at 20°C

[Peak areas normalized to di- <i>n</i> -propyl ether]							
	CH <sub>3</sub> CHO	MeOEt	C <sub>2</sub> H <sub>5</sub> CHO	MeOPr <sup>n</sup>	(EtOBu <sup>i</sup> - EtOBu <sup>n</sup> )	Pr <sup>i</sup> OPr <sup>n</sup>	EtOBu <sup>n</sup>
	0.45	0.14	(0.21)	0.29	2.95	1.32	1.11
	—	0.10	0.47	0.26	2.22	1.22	1.19
	0.44	0.13	0.37	0.24	2.30	1.30	1.22
	0.31	0.10	0.31	0.21	2.24	(1.08)	1.17
	0.32	0.10	0.47	0.23	2.17	1.17	(1.02)
	—	0.12	0.33	(0.51)	2.50	(1.75)	1.11
Av.	0.38	0.11	0.38	0.25	Varies	1.25	1.16
Av molar ratio:	0.62	0.20	0.50	0.30	—	1.32	0.87

Table 3—Bond Reactivities of Different Bonds in Ethyl *n*-Propyl Ether

Bond attacked (No. of identical bonds)	Product formed (X)	Standard product (S)	20°C		100°C	
			Amount X/S	Bond reactivity	Amount X/S	Bond reactivity
Primary in Pr <sup>n</sup> (3)	EtOBu <sup>n</sup>	Pr <sup>n</sup> OPr <sup>n</sup> (3)	0.92	0.92	0.87	0.87
Sec. in Pr <sup>n</sup> (2)	EtOBu <sup>n</sup>	Pr <sup>n</sup> OPr <sup>n</sup> (3)	0.86	1.29	2.30	3.50
Sec. in Pr <sup>n</sup> (2)	EtOBu <sup>i</sup>	Pr <sup>n</sup> OPr <sup>n</sup> (3)	1.16	1.74	—	—
Pr—O (1)	MeOEt	Pr <sup>n</sup> OPr <sup>n</sup> (3)	0.24	0.72	0.20	0.60
Primary in C <sub>2</sub> H <sub>5</sub> (3)	Pr <sup>n</sup> OPr <sup>n</sup>	Pr <sup>n</sup> OPr <sup>n</sup> (3)	1.00	1.00	1.00	1.00
Sec in C <sub>2</sub> H <sub>5</sub> (2)	Pr <sup>i</sup> OPr <sup>n</sup>	Pr <sup>n</sup> OPr <sup>n</sup> (3)	1.22	1.83	1.32	1.98
Et—O (1)	MeOPr <sup>n</sup>	Pr <sup>n</sup> OPr <sup>n</sup> (3)	0.37	1.11	0.30	0.90

attack at secondary  $\alpha$ C—H and  $\beta$ C—H bonds of propyl group of this ether, which are attacked 1.74 and 1.29 times, respectively. The descending order of the reactivity of C—H bonds is  $\alpha > \beta > \gamma$ . The higher rate of attack on  $\alpha$  secondary bond is possibly due to its proximity to the electrophilic oxygen. The known preference of attack on primary C—H of dimethyl ether over that of diethyl ether when compared to that of propyl group in ethyl propyl ether shows the bond reactivities in the order 1.72, 1.00, and 0.92, respectively. This indicates the electrophilic effect of oxygen being operative.

The effect of temperature on these reaction is small, and within experimental error, it shows that the activation energy difference between different insertion reactions is at most 100 cal. The results agree with those of other workers<sup>3</sup> who have shown that the activation energy for insertion of methylene into primary bonds of alkanes is slightly different from that for insertion in secondary or tertiary bond. However,

the relative *A*-factors cancel out this difference so that the relative rate of attack is approximately, but not exactly, statistical. These results obtained in gas phase contrasted with those of Doering and co-workers<sup>3</sup> who found that in the liquid phase the insertion reactions with both ethers and hydrocarbons were indiscriminate. The present results confirm again the difference between the gas and liquid phase reactions.

The displacement reaction products show the bond reactivities of Et—O as 0.90 at 20° and 1.11 at 100°C whereas those for Pr—O, the values are 0.60 at 20° and 0.72 at 100°C. The lower value for Pr—O compared to Et—O indicates steric hindrance. The values for Pr—O is still lower (0.54) at 100°C (unpublished data).

#### References

- 1 Mehta R K S, *Indian J Chem*, **24B** (1985) 1239.
- 2 Mehta R K S, *Indian J Chem*, **25B** (1986) 111.
- 3 Doering W, Buttery R G, Laughlin R G & Chaudhary N, *J Am chem Soc*, **78** (1956) 3224.
- 4 Knox J & Trotman-Dickenson A, *Chem Ind*, (1957) 731.

## Mass Spectra of Benzamidoxime & Its O-Methyl Derivative

RAJENDRA MOHAN SRIVASTAVA\* & THEREZA MAIA BELTRÃO†

Departamento de Química Aplicada, Universidade Federal de Pernambuco, Cidade Universitária, 50.000-Recife, PE, Brazil  
and

LAWRENCE T NIELSEN‡

Instituto de Química, Universidade Estadual de Campinas, Campinas, São Paulo, Brazil

Received 17 October 1984; accepted 18 March 1985

Benzamidoxime (**1**), benzamidoxime- $d_3$  (**2**) and its O-methyl derivative (**3**) have been examined by low and high resolution electron-impact mass spectrometry. Mass-analysed ion kinetic energy spectra (MIKES) of the principal ions of **1** and **3** provide information about fragmentation pathways. Some interesting fragmentation differences between **1** and **3** and the previously reported pyridylamidoximes are discussed.

The low resolution mass spectra of various N-substituted benzamidoximes,  $^1\text{N}$ -phenylbenzamidoxime and its deuterium analogs<sup>2</sup> and 2-, 3- and 4-pyridylamidoximes and their O-trimethylsilyl derivatives<sup>3</sup> have been reported. We present, in this paper, results of studies on low and high resolution mass spectra of the parent benzamidoxime (**1**), its deuterated analog (**2**) and its O-methyl derivative (**3**), including the mass-analysed ion kinetic energy spectra (MIKES) of **1** and **3**. These results have been compared with the previously reported work. Literature records the mass spectrum of **1** without comments<sup>4</sup>.

### Materials and Methods

Low resolution mass spectra of **1** and **2** were obtained on KRATOS MS 25 and of **3** on Hitachi-Perkin-Elmer RMU-7 MG double focussing mass spectrometers at 70 eV employing direct insertion probe. The sample temperature in all the cases was 80°C. Source temperatures of 150°, 200° and 250°C were used for **1** and **2**. The source temperature for **3** was 100°C. The MIKES results of **1** and **3** were obtained on a Varian MAT 311A mass spectrometer. A resolution of 10,000 (10% valley definition) was employed for exact mass measurements.

Compound (**2**) was prepared by recrystallization (twice) of pure **1** from deuterium oxide. The compounds (**1**) and (**3**) were synthesized by the procedure described earlier<sup>5</sup>.

### Results and Discussion

#### Benzamidoxime (**1**)

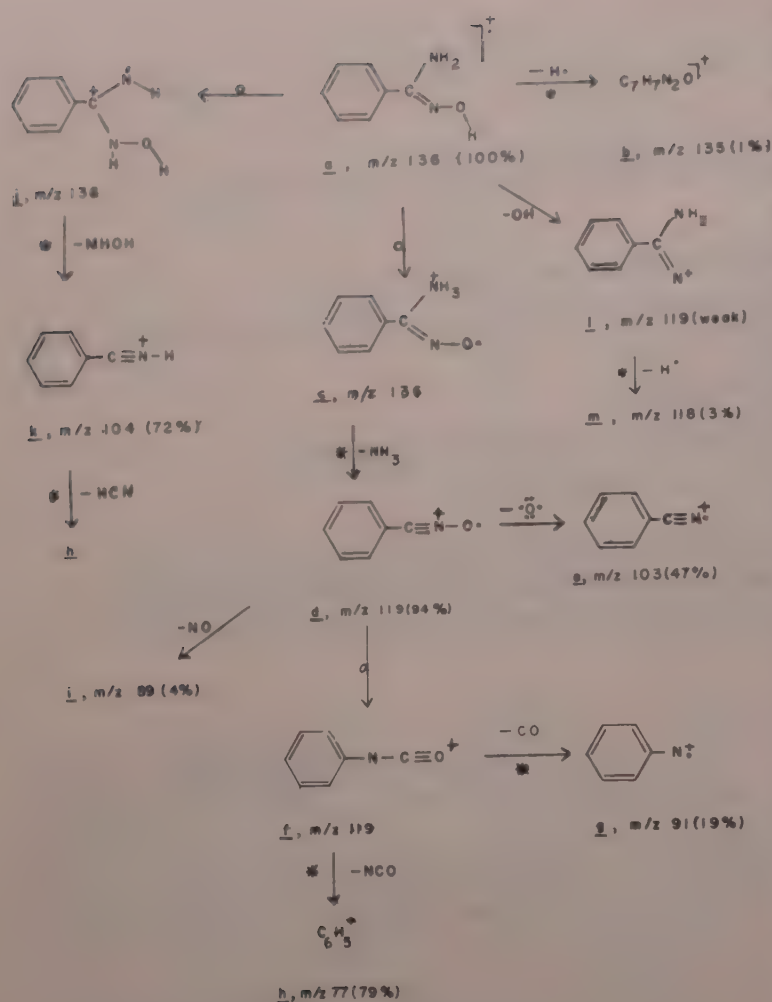
†Taken in part from the MS thesis (1976) of the author.  
‡Present address: Rhodia Research Center, Fazenda São Francisco-CP7, Paulínia, São Paulo, Brazil.

The relative intensities of principal ions of **1** under low resolution mass spectrometry at the source temperature of 150°C are:  $m/z$  137 (8%), 136 (100), 135 (1), 120 (17), 119 (94), 118 (3), 105 (18), 104 (72), 103 (47), 91 (19), 89 (4), 77 (79), 76 (23), 64 (16), 51 (48), 50 (27) and 39 (13).

Compound (**1**) exhibits the molecular ion (base peak) at  $m/z$  136 which on the basis of the observed metastable ion pathways, should exist in at least three forms: ion (*a*), and the rearranged ions (*c*) and (*j*) (Scheme 1). The molecular ion (*a*), as supported by MIKES, loses H weakly to furnish the ion *b* and  $\text{NH}_3$  strongly to give benzonitrile oxide ion by hydrogen transfer:  $a \rightarrow c \rightarrow d$ . Benzonitrile oxide ion loses either oxygen atom or NO by direct cleavage to give ions (*e*) and (*i*) respectively. Ion (*d*) rearranges and loses CO, an observation also recorded for the loss of CO from benzonitrile oxide itself<sup>6</sup>.

The weakly intense ion at  $m/z$  118, which is shown by high resolution technique, has an elemental composition  $\text{C}_7\text{H}_6\text{N}_2^+$ . The origin of this ion can be inferred from the observed metastable transition from ion (*l*). The peak at  $m/z$  119 is predominantly due to the radical cation,  $\text{C}_7\text{H}_5\text{NO}^{\cdot+}$  (Found: 119.0363, 119.0372. Calc.: 119.0372), and only a small fraction of  $m/z$  119 is presumed to be  $\text{C}_7\text{H}_7\text{N}_2^+$ . The logical source of ions (*l*) and (*m*) is the molecular ion. The rearranged molecular ion (*j*) loses  $-\text{NHOH}$  as seen by MIKES to provide protonated benzonitrile ion, which in turn affords the fragment (*h*).

It is assumed that the ion (*d*) affords a species at  $m/z$  103 ( $\text{C}_7\text{H}_5\text{N}^+$ ). Selva *et al.*<sup>6</sup> examined benzonitrile oxide under electron impact and observed the formation of benzonitrile ion. The fragment *i* ( $m/z$  89) occurs with relative abundance of 4% and it is believed that it originates from ion (*d*) as previously reported<sup>6</sup> in



Scheme 1: Fragmentation pathways of benzamidoxime

the case of benzonitrile oxide. Electron impact fragmentation of pyridylamidoximes<sup>3</sup> gives pyridine ion ( $m/z$  79) as a rearranged product from the molecular ion. A similar process does not occur with **1** as shown by the lack of ion at  $m/z$  78.

The mass spectrum of **1** shows significant intensity changes for the  $m/z$  120 and 103 ions with change in source temperature. At  $150^\circ$ , the ratio of intensities of  $m/z$  119 and 120, i.e. of a non-thermally dependent ion to a thermally dependent ion is 1.0:0.18; at  $200^\circ$  and  $250^\circ$ , the ratios are 1.0:0.33 and 1.0:1.6 respectively. The  $m/z$  120 ion is shown by high resolution as  $C_7H_8N_2^+$  (Found: 120.0670, 120.0686. Calc.: 120.0685) which is consistent with the benzamidine structure. High source temperatures, therefore, produce high concentration of neutral benzamidine in the gas phase which gets ionized furnishing ions at  $m/z$  120 and 103 by fragmentation. This thermal process involves a proton transfer to nitrogen before the loss of oxygen. A similar process has been reported by Pearse and Jacobsson<sup>3</sup>.

#### Benzamidoxime- $d_3$ (**2**)

Relative intensities of principal fragments of **2** under low resolution mass spectrometry at the source temperature of  $150^\circ$  are:  $m/z$  140 (3%), 139 (36), 138 (69), 137 (51), 136 (14), 123 (3), 122 (5), 121 (4), 120 (14),

119 (100), 118 (2), 107 (3), 106 (14), 105 (42), 104 (23), 103 (28), 102 (2), 91 (19), 89 (3), 77 (58), 64 (13), 51 (32), 50 (17) and 39 (8).

We examined the fragments at  $m/z$  121, 122 and 123 of **2** by high resolution mass spectrometry which provided the composition of these as  $C_7H_7DN_2^+$  (Found: 121.0718. Calc.: 121.0748),  $C_7H_6D_2N_2^+$  (Found: 122.0800, Calc.: 122.0811) and  $C_7H_5D_3N_2^+$  (Found: 123.0865, Calc.: 123.0874) respectively. These apparently arise by the thermal loss of oxygen from neutral species of  $C_7H_7DON_2$ ,  $C_7H_6D_2ON_2$  and  $C_7H_5D_3ON_2$  respectively followed by ionization. The loss of  $-ND_3$  from the molecular ion of **2** also supports the route  $c \rightarrow d$ . The peaks at  $m/z$  139 (36), 138 (69), 137 (51) and 136 (14) are molecular ions corresponding to tri-, di- and mono-deuterated species and non-deuterated compound. The sum of the relative intensities of these four molecular ions is 170% while in the sample these are present to the extent of 21, 41, 30 and 8% respectively. Ions at  $m/z$  123 (3%), 122 (5), 121 (4) and 120 (14) are mostly the thermal decomposition products of tri-, di-, mono- and non-deuterated neutral compounds respectively. The new relative intensities based on the sum of the molecular ions of non-deuterated and possible deuterated forms, viz., 170% are:  $m/z$  136 (100%), 120 (15), 119 (59), 107 (2), 106 (8), 104 (39), 103 (16), 102 (1), 91 (11), 89 (2), 77 (34), 64 (8), 51 (19), 50 (10) and 39 (5). The peaks at  $m/z$  136, 120 and 104 represent the sum of non-deuterated and possible deuterated forms.

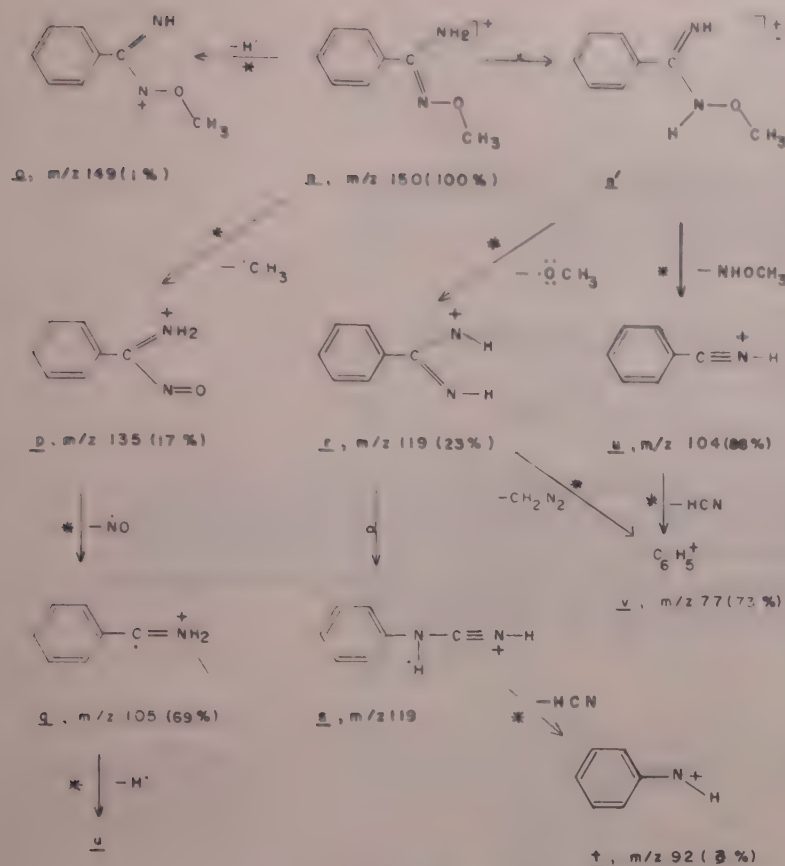
#### O-Methylbenzamidoxime (**3**)

We examined the mass spectrum of **3** with a view to comparing the fragmentation pathways of **1** and **3** and have observed significant differences.

The relative intensities of principal ions of **3** under low resolution mass spectrometry are:  $m/z$  151 (11), 150 (100), 149 (1), 135 (17), 119 (23), 105 (69), 104 (88), 103 (27), 92 (3), 91 (9), 77 (73), 64 (8), 63 (8), 51 (58), 50 (27) and 39 (19).

Compound (**3**) showed the molecular ion at  $m/z$  150 as the base peak (100%) (see Scheme 2). MIKES revealed that the molecular ion ( $n$ ) produces four daughter ions, viz.,  $o$ ,  $p$ ,  $r$  and  $u$  respectively. The fragment  $o$  (1%) originates from  $n$  by the loss of a hydrogen radical. The ion ( $n$ ) after losing the methyl radical forms  $p$  which in turn ejects NO to give the fragment  $q$  at  $m/z$  105 which goes to  $u$ . There is an ion at  $m/z$  103 whose origin is still unknown.

The methoxy radical is lost from the molecular ion to furnish  $m/z$  119. This species is assigned the structure as shown in  $r$  and corresponds to the formula  $C_7H_7N_2^+$  as supported by the high resolution work (theoretical and observed values are 119.0580 and 119.0606


 Scheme 2 : Fragmentation pathways of *O*-methylbenzamidoxime.

respectively). Finally, *r* provides two daughter fragments—one at  $m/z$  77 ( $C_6H_5^+$ ) by direct cleavage and the other at  $m/z$  92 ( $C_6H_6N^+$ ) possibly through structure (*s*). This kind of rearrangement has been reported earlier<sup>7</sup>. Also, the production of protonated benzonitrile (*u*) is from *n'*.

The results presented herein show that it is the oxygen atom which is lost from **1** by a thermal process.

The ion at  $m/z$  119 is due to benzonitrile oxide ( $C_7H_5NO^+$ ) and not due to  $C_7H_7N_2^+$ . *O*-Methylbenzamidoxime (**3**) also affords a species at  $m/z$  119 but its composition is  $C_7H_7N_2^+$ . In pyridylamidoxime, ejection of  $NH_2CNO$  to give pyridine fragment ( $m/z$  79) is shown to be a common pathway<sup>3</sup>. However, no corresponding ion ( $m/z$  78) has been observed in benzamidoxime (**1**). *O*-Methylbenzamidoxime offers different fragmentation mode on electron impact than the parent benzamidoxime.

### Acknowledgement

The authors express their gratitude to the Brazilian Research Council (CNPq) for financial assistance, to Dr. C Kascheres, Instituto de Quimica, UNICAMP, Campinas, and to Dr B C Das of ICSN/CNRS, Gif sur Yvette, for measuring the exact masses of some ions of **1**, to Prof. A McKillop, School of Chemical Sciences, University of East Anglia, Norwich, England, for the low and high resolution mass spectral data of compounds **1** and **2** and to Dr T H Müller for the high resolution spectrum and the elemental composition of most of the ions of **3**.

### References

- 1 Micromastoras E D, Argyropoulos N G & Alexadrou N E, *Chimica Chronica, New Series*, **3** (1974) 133.
- 2 Hemalatha D & Kallury R K M R, *Org Mass Spectrom*, **11** (1976) 347.
- 3 Pearse (Jr) G A & Jacobsson S, *Org Mass Spectrom*, **15** (1980) 331.
- 4 Ooi N S & Wilson D A, *J chem Soc Perkin-II*, (1980) 1792.
- 5 Beltrão T M & Srivastava R M, *An Acad Bras Ciênc*, **50** (1978) 159.
- 6 Selva A, Zerilli L F, Cavalleri B & Gallo G G, *Org Mass Spectrom*, **6** (1972) 1347.
- 7 Srivastava R M, *Org Mass Spectrom*, **13** (1978) 14.

## Chemical Ionization Mass Spectra of 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octanes†

K P MADHUSUDANAN\*, KHALID A KHAN & ABOO SHOEB

Central Drug Research Institute, Lucknow 226 001

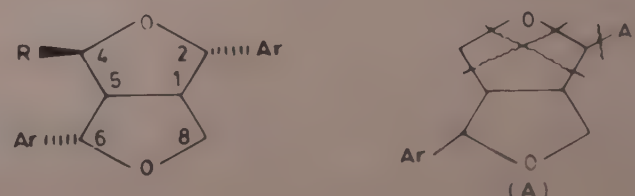
Received 20 November 1984; accepted 25 February 1985

A study of the chemical ionization mass spectra of a few 2,6-diaryl-3,7-dioxabicyclo-[3.3.0]octanes (1-5) using  $\text{CH}_4$ ,  $\text{D}_2\text{O}$ ,  $\text{NH}_3$  and  $\text{MeNH}_2$  has shown that even under CI conditions these molecules suffer considerable fragmentation giving rise to structurally diagnostic ions. The fragmentation pathways have been elucidated with the help of  $\text{D}_2\text{O}$  CI spectra. Abundant adduct ions could be obtained only with  $\text{NH}_3$  or  $\text{MeNH}_2$  as the reagent gas. However, under these conditions, the 4-substituted compounds have been found to undergo substitution in the 4-substituent with  $\text{NH}_2$  or  $\text{NHCH}_3$ .

Application of electron impact mass spectrometry in the structure elucidation of naturally occurring 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes is fairly well established<sup>1-3</sup>. These molecules undergo extensive fragmentation resulting from multiple bond cleavages giving rise to complex spectra. Thus, it seemed desirable to consider the application of chemical ionization mass spectrometry in their structure elucidation. Further, so far there has been no report on the chemical ionization mass spectra of these compounds. In this investigation we have studied the chemical ionization mass spectra of the following 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes, viz. sesamin (1), pinoresinol (2), 4-hydroxypinoresinol (3), 4-hydroxyeudesmin (4) and 4-methoxyeudesmin (5).

The abundances of the major ions in the methane CI spectra of 1-5 are given in Table 1. The spectra of 1-5 were also obtained under  $\text{D}_2\text{O}$  CI conditions (Fig. 1). With the help of these spectra it was possible to elucidate the CI induced fragmentation pathways of these compounds even though all these molecules underwent considerable fragmentation under the CI conditions employed.

The molecular ion region shows three peaks, viz.  $(\text{MH})^+$ ,  $\text{M}^+$  and  $(\text{M}-\text{H})^+$ . The comparatively higher abundance of molecular ions is rather unusual under  $\text{CH}_4$  CI conditions. The  $(\text{M}-\text{H})^+$  ion would formally correspond to the oxonium ion formed by the removal of  $\alpha\text{-H}$  from the tetrahydrofuran nucleus (Scheme 1). This is further confirmed by the  $\text{D}_2\text{O}$  CI spectra which show  $(\text{MD}-\text{HD})^+$  ions. Compounds 1 and 2 show abundant  $(\text{MH}-\text{H}_2\text{O})^+$  ion at  $m/z$  337 and 341 respectively. The  $\text{D}_2\text{O}$  CI spectra of these compounds (Fig. 1) show both  $(\text{MD}-\text{HDO})^+$  and  $(\text{MD}-\text{H}_2\text{O})^+$  ions suggesting the loss of water by two processes, viz.



- |   |   |  |                        |
|---|---|--|------------------------|
| 1 | $\text{R} = \text{H}$ , $\text{Ar} =$   |  | (SESAMIN)              |
| 2 | $\text{R} = \text{H}$ , $\text{Ar} =$   |  | (PINORESINOL)          |
| 3 | $\text{R} = \text{OH}$ , $\text{Ar} =$  |  | (4-HYDROXYPINORESINOL) |
| 4 | $\text{R} = \text{OH}$ , $\text{Ar} =$  |  | (4-HYDROXY EUDESMIN)   |
| 5 | $\text{R} = \text{OMe}$ , $\text{Ar} =$ |  | (4-METHOXY EUDESMIN)   |

direct elimination of  $\text{H}_2\text{O}$  from the  $\text{MH}^+$  ion and protonation of a thermally formed neutral molecule. The hydrogen atom(s) lost could originate from either C-1 or C-4 (Scheme 1).

In the 4-substituted compounds (3-5), the substituent is lost, either as  $\text{H}_2\text{O}$  or  $\text{MeOH}$ , prior to further fragmentation. This is understandable in view of the labile nature of protonated acetals. The  $\text{D}_2\text{O}$  CI spectra in this case also show both  $(\text{MD}-\text{RD})^+$  and  $(\text{MD}-\text{RH})^+$  ions, the latter resulting from the protonation of a thermally formed neutral fragment (Scheme 2a). The  $(\text{MH}-\text{RH})^+$  ion further loses a molecule of  $\text{H}_2\text{O}$  giving rise to  $(\text{MH}-\text{RH}-\text{H}_2\text{O})^+$  ion.

Loss of  $\text{CH}_2\text{O}$  occurs only from the  $(\text{MH}-\text{RH})^+$  ions in 3-5 (Scheme 2a) while in 1 and 2 the  $\text{MH}^+$  ion directly loses  $\text{CH}_2\text{O}$  (Scheme 1). As expected, the  $\text{D}_2\text{O}$  CI spectra of 3-5 show two peaks corresponding to  $(\text{MD}-\text{RD}-\text{CH}_2\text{O})^+$  and  $(\text{MD}-\text{RH}-\text{CH}_2\text{O})^+$  ions. Elimination of the C-4 substituent as a neutral

†CDRI Communication No. 1622

Table 1 — Ion Abundances (%) in the CH<sub>4</sub> CI Spectra of 1-5

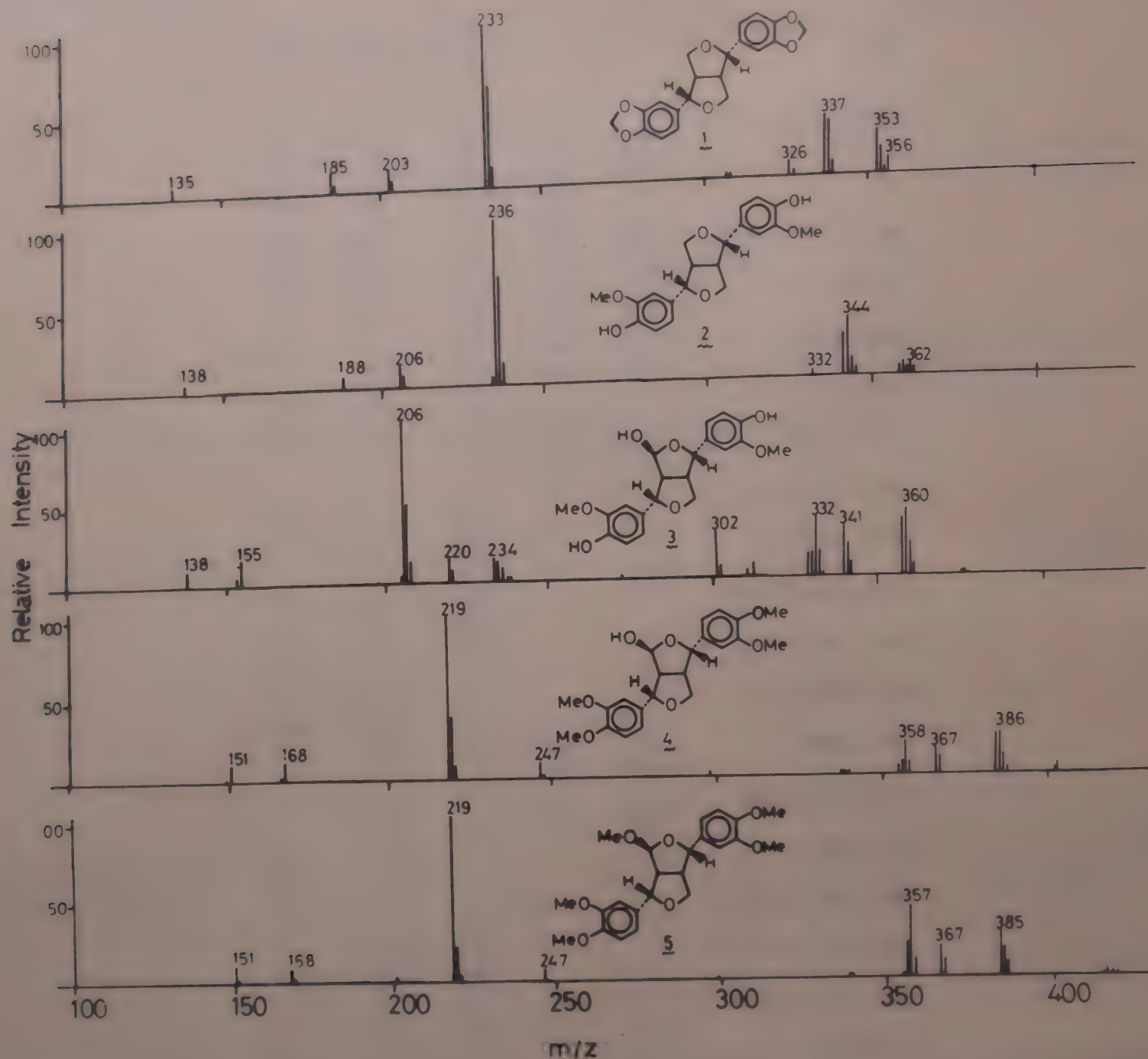
Ion	Compound				
	1	2	3	4	5
M.C <sub>2</sub> H <sub>5</sub> <sup>+</sup>	383 (9.8)	387 (4.0)	403 (2.5)	431 (5.0)	445 (7.3)
MH <sup>+</sup>	355 (31.3)	359 (15.3)	375 (7.1)	403 (17.1)	417 (6.8)
M <sup>+</sup>	354 (28.5)	358 (28.1)	374 (5.3)	402 (3.5)	416 (4.8)
(M - H) <sup>+</sup>	353 (24.5)	357 (41.2)	373 (3.5)	401 (7.9)	415 (6.9)
(MH - H <sub>2</sub> O) <sup>+</sup>	337 (35.7)	341 (68.6)	357 (18.5)	385 (16.9)	—
(MH - RH) <sup>+</sup>	—	—	357 (18.5)	385 (16.9)	385 (14.6)
(MH - CH <sub>2</sub> O) <sup>+</sup>	325 (21.0)	329 (6.9)	—	—	—
(MH - RH - H <sub>2</sub> O) <sup>+</sup>	—	—	339 (12.9)	367 (10.3)	367 (7.0)
(MH - H <sub>2</sub> O - CH <sub>2</sub> O) <sup>+</sup>	307 (12.7)	311 (8.4)	327 (13.6)	355 (8.8)	—
(MH - RH - CH <sub>2</sub> O) <sup>+</sup>	—	—	327 (13.6)	355 (8.8)	355 (6.4)
(MH - RH - H <sub>2</sub> O) <sup>+</sup>	—	—	339 (12.9)	367 (10.3)	367 (7.0)
(MH - RH - CO) <sup>+</sup>	—	—	329 (9.3)	357 (9.9)	357 (20.3)
(MH - ArH) <sup>+</sup>	233 (100)	235 (100)	251 (2.0)	265 (2.5)	279 (5.3)
(MH - H <sub>2</sub> O - ArH) <sup>+</sup>	215 (6.0)	219 (14.1)	233 (27.7)	247 (18.0)	—
(MH - RH - ArH) <sup>+</sup>	—	—	233 (27.7)	247 (18.0)	247 (9.4)
(MH - RH - ArCH <sub>3</sub> ) <sup>+</sup>	—	—	219 (8.1)	233 (4.5)	—
(MH - RH - ArCHO) <sup>+</sup>	—	—	205 (100)	219 (100)	219 (100)
(MH - ArCH <sub>2</sub> OH) <sup>+</sup>	203 (68.2)	205 (33.2)	221 (2.0)	235 (2.0)	—
ArCHOH <sup>+</sup>	151 (6.6)	—	153 (14.6)	167 (18.4)	167 (7.6)
ArCH <sub>2</sub> <sup>+</sup>	135 (50.9)	137 (15.8)	137 (31.3)	151 (26.9)	151 (23.3)

molecule induces loss of CO (Scheme 2a). This pathway is not observed in **1** and **2**.

The base peaks in the spectra of **1** and **2** correspond to (MH - ArH)<sup>+</sup> ions. The observation of two peaks corresponding to this process, (MD - ArD)<sup>+</sup> and (MD - ArH)<sup>+</sup>, in the D<sub>2</sub>O CI spectra suggests the operation of more than one mechanism for this process. Protonation of the aromatic ring followed by heterolytic cleavage of the bond between C-2 or C-6 and aryl moiety could lead to (MD - ArD)<sup>+</sup> ion. Loss of ArD subsequent to initial deuterium transfer to the furan oxygen could also lead to (MD - ArD)<sup>+</sup> ion having oxonium ion structure. However, if the hydrogen lost originates from C-1 or C-5, D<sub>2</sub>O CI spectrum would show (MD - ArH)<sup>+</sup> ions. This can be

visualised as resulting from the protonation of a thermally formed neutral fragment. These processes are illustrated in Scheme 1b. In the 4-substituted compounds **3-5** the loss of ArH occurs only from the (MH - RH)<sup>+</sup> ion. The most intense ion in the spectra of **3-5** corresponds to (MH - RH - ArCHO)<sup>+</sup>.

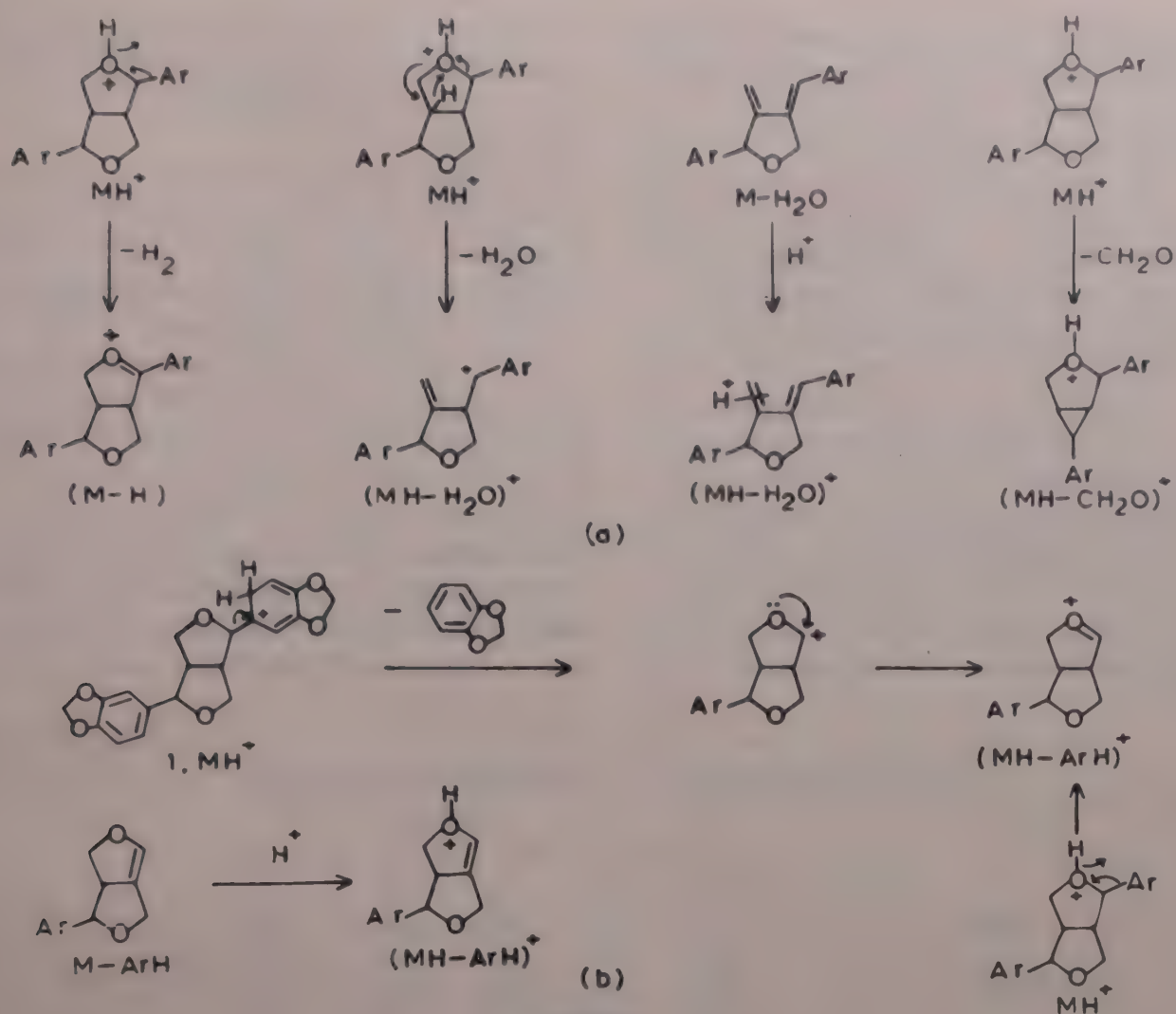
The (MH - ArCH<sub>2</sub>OH)<sup>+</sup> ion is prominent only in **1** and **2**. The presence of ArCH<sub>2</sub><sup>+</sup> ion in the spectra of all these compounds helps in identifying the aryl group. The D<sub>2</sub>O CI spectra also indicate the number of replaceable hydrogens in the aryl groups. Compounds containing hydroxy groups on the aromatic ring could be expected to undergo deuterium exchange of the aromatic hydrogens *ortho* and *para* to the hydroxyl groups also<sup>4,5</sup>. Such an exchange in these lignans


 Fig. 1 -  $D_2O$  CI mass spectra of 2,6-diaryl-3,7-dioxabicyclo-[3.3.0]octanes (1-5).

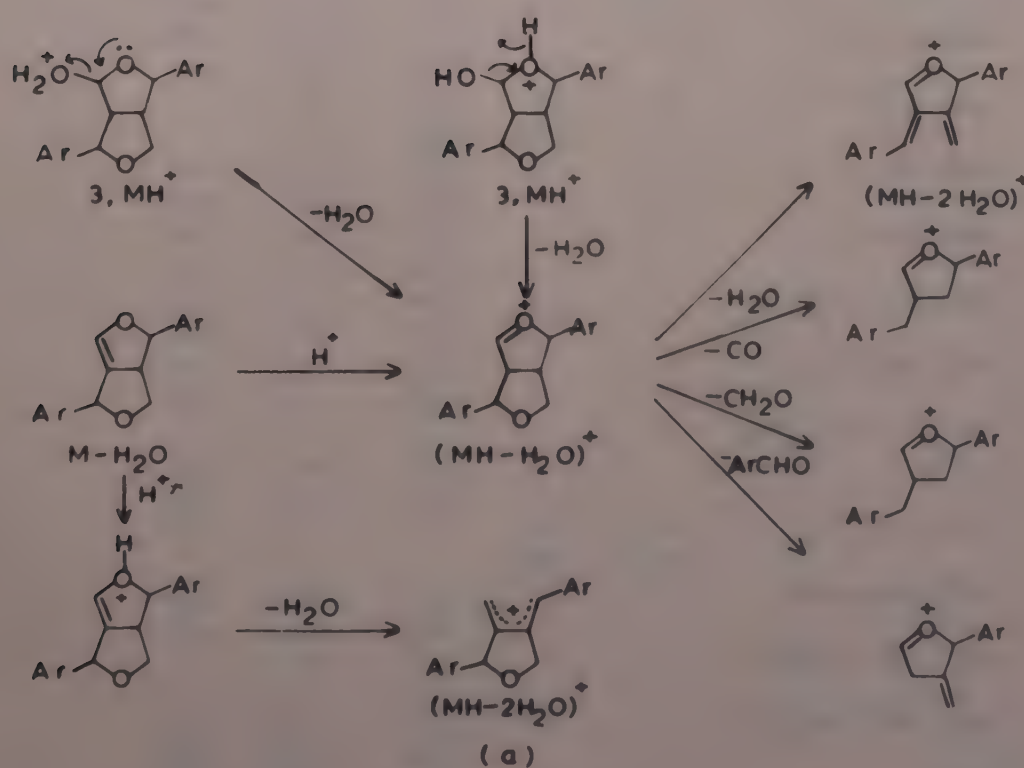
would be reflected by a shift in the  $m/z$  values of the  $ArCH_2^+$  ions. The  $D_2O$  CI spectra of 1-5 clearly show that the aromatic hydrogens do not undergo exchange under the  $D_2O$  CI conditions employed in the present study.

It may be noted here that the  $CH_4$  and  $D_2O$  CI spectra fail to show unambiguously the protonated molecular ion in contrast to the high abundance of the molecular ions in their EI spectra. It appears that protonation under the conditions employed for CI is sufficiently exothermic and leads to facile fragmentation of these molecules. Lowering the source temperature from 200 to 150  $^{\circ}C$  did not help much in reducing the fragmentation, particularly in 3. However, it must be emphasised that the fragments thus produced are structurally diagnostic. Nevertheless, the absence of a prominent molecular species for

the unambiguous determination of the molecular weights of these compounds is a limiting factor. Use of a reagent gas with higher proton affinity might help in obtaining an intense molecular species. The CI spectra of 1-5 were recorded using  $NH_3$  as the reagent gas and the ion abundances in these spectra are given in Table 2. Though the compounds 1 and 2 give abundant  $NH_4^+$ -adduct ions at 200  $^{\circ}C$ , the 4-hydroxy compounds 3 and 4 do not yield a significant  $MNH_4^+$  ion peak even at 150  $^{\circ}C$ . With a few exceptions most of the fragmentation pathways under  $CH_4$  and  $NH_3$  CI conditions are similar. The  $NH_4^+$ -adduct ion decomposes by the loss of  $NH_3$  and  $H_2O$ . The loss of  $NH_3$  results in  $MH^+$  ion while elimination of  $H_2O$  leads to a substitution ion having the same nominal mass as  $M^+$  (Scheme 2b). Reducing the ion source temperature or increasing the  $NH_3$  pressure resulted in



SCHEME 1



SCHEME 2

an increase in the abundance of the substitution ion. Both  $S_N1$  and  $S_N2$  reactions have been proposed for the formation of substitution ions in the  $NH_3$  CI spectra of certain alcohols<sup>6-10</sup>. However, only the  $S_N2$  mechanism has been clearly shown using diastereoisomeric alcohols<sup>7,10</sup>. The 4-methoxy derivative **5** showed both  $(MNH_4 - MeOH)^+$  and  $(MNH_4 - H_2O)^+$  ions, the former corresponding to substitution of OMe with  $NH_2^{11}$ . The loss of  $H_2O$  from  $MNH_4^+$  is common to all the lignans (**1-5**). In the absence of data from  $ND_3$  CI and metastable spectra elucidation of the mechanisms of these substitution reactions is not possible.

Since, even with  $NH_3$ , the 4-hydroxy compounds **3** and **4** did not show significant  $MNH_4^+$  ion peak the spectra of **3-5** were recorded using methyl amine, a stronger base, as the reagent. Table 3 shows the ion abundances in the spectra of **3-5**. The base peaks now

correspond to the adduct ion which loses RH to give the substitution ion. The abundant substitution ion in **3** undergoes further fragmentation by the loss of CO and  $CH_2O$ .

A comparison of the EI and CI spectra reveals that whereas the base peaks in the EI spectra of **1-5** correspond to the respective  $ArCO^+$  ions, the CI spectra of **1-2** and **3-5** are characterised by the presence of base peaks corresponding to  $(MH - RH)^+$  and  $(MH - RH - ArCHO)^+$  ions respectively. The  $D_2O$  CI spectra reveal that there is a substantial contribution from thermal processes in the observed fragment ions. Most of the total ion current in the EI spectra is carried by lower mass fragments while in the CI spectra higher mass fragments predominate. However, it is interesting to note the similarity of bond cleavages in these lignans under both EI and CI conditions (see structure A). It also transpires from the above results that in the CI

Table 2—Ion Abundances (%) in the  $NH_3$  CI Spectra of **1-5**

Ion	Compound				
	1	2	3	4	5
$MNH_4^+$	372 (100)	376 (50.6)	392 (2.0)	420 (2.0)	434 (6.2)
$MH^+$	355 (9.6)	359 (15.6)	375 (5.0)	403 (5.8)	417 (3.7)
$(MNH_4 - H_2O)^+$	354 (10.0)	358 (17.2)	374 (19.7)	402 (14.0)	416 (8.0)
$(MNH_4 - RH)^+$	—	—	374 (19.7)	402 (14.0)	402 (13.3)
$(MH - H_2O)^+$	337 (22.1)	341 (63.5)	357 (95.4)	385 (42.5)	—
$(MH - RH)^+$	—	—	357 (95.4)	385 (42.5)	385 (68.3)
$(MH - RH - H_2O)^+$	—	—	339 (24.1)	367 (14.1)	367 (17.1)
$(MH - RH - CO)^+$	—	—	329 (16.3)	357 (6.3)	357 (20.8)
$(MH - RH - CH_2O)^+$	—	—	327 (27.8)	355 (4.8)	355 (3.0)
$(MH - RH - H_2O - CO)^+$	—	—	311 (19.6)	339 (4.8)	339 (4.2)
$(MH - ArH)^+$	233 (46.1)	235 (100)	—	—	—
$(MH - RH - ArH)^+$	—	—	233 (9.1)	247 (6.4)	247 (8.9)
$(MH - RH - ArCH_3)^+$	—	—	219 (9.5)	233 (3.0)	—
$(MH - RH - ArCHO)^+$	—	—	205 (100)	219 (100)	219 (100)
$ArCH_2^+$	—	137 (4.5)	137 (8.0)	151 (6.7)	151 (4.9)
$(MNH_4 - ArH)^+$	250 (8.6)	252 (16.4)	—	—	—
$(MNH_4 - RH - ArCHO)^+$	—	—	222 (8.2)	236 (9.8)	236 (27.6)

Table 3 – Ion Abundances (%) in the MeNH<sub>2</sub> CI Spectra of 3-5

Ion	Compound		
	3	4	5
(M + MeNH <sub>3</sub> ) <sup>+</sup>	406 (100)	434 (100)	448 (100)
(M + MeNH <sub>3</sub> - RH) <sup>+</sup>	388 (64.3)	416 (36.4)	416 (5.4)
(M + MeNH <sub>3</sub> - RH - CO) <sup>+</sup>	360 (41.2)	—	—
(M + MeNH <sub>3</sub> - RH - CH <sub>2</sub> O) <sup>+</sup>	358 (27.7)	—	—

spectra of the lignans 1-5, fragment ion or adduct ion formation could be selected by the appropriate choice of the reagent gas and ion source conditions.

### Experimental Procedure

The compounds used in this study were natural products isolated from *Lonicera hypoleuca*<sup>12</sup> and *Artemisia roxburghiana*<sup>13</sup> and their derivatives. The CI mass spectra were recorded on a Jeol D-300 mass spectrometer having combined EI/CI source and attached to JMA-2000 data system. D<sub>2</sub>O used was obtained from Merck, Sharp and Dohme, Canada and was of purity > 99 %. A 40 % solution of methyl amine in water was used as the source of methyl amine. The source housing pressure was  $1.5 \times 10^{-5}$  torr. The other

ion source conditions were: electron energy, 200 eV; emission current, 300  $\mu$ A; and temperature, 200°C (unless otherwise specified). The samples were introduced through the direct inlet system and heated to 200 °C.

### Acknowledgement

The authors are grateful to RSIC, Lucknow where the mass spectral studies were carried out.

### References

- 1 Pelter A, *J chem Soc (C)*, (1967) 1376.
- 2 Pelter A & Ward R S, in *Chemistry of lignans*, edited by C B S Rao (Andhra University Press, Waltair) 1978, 227.
- 3 Anjaneyulu A S R, Rao A M, Rao V K, Row R L, Pelter A & Ward R S, *Tetrahedron*, **33** (1977) 133.
- 4 Hunt D F & Sethi S K, *J Am chem Soc*, **102** (1980) 6953.
- 5 Madhusudan K P, Sachdev K, Harrison D A & Kulshreshtha D K, *Int J Mass Spec Ion Processes*, **62** (1984) 289.
- 6 Keough T & DeStefano A J, *Org Mass Spectrom*, **16** (1981) 527.
- 7 Bastard J, Manh D D K, Fetizon M, Tabet J C & Fraisse D, *J chem Soc Perk-II*, (1981) 1591.
- 8 Tecon P, Hirano Y & Djerassi C, *Org Mass Spectrom*, **17** (1982) 277.
- 9 Gulacar F O, Mermoud F, Winkler F J & Buchs A, *Helv Chim Acta*, **67** (1984) 488.
- 10 Tabet J C, Bertranne M, Beloeil J C & Stahl D, *Org Mass Spectrom*, **19** (1984) 363.
- 11 Tabet J C, Tondeur Y, Hirano Y, Wegmann A, Tecon P & Djerassi C, *Org Mass Spectrom*, **19** (1984) 473.
- 12 Khan K A & Shoeb A, *Phytochemistry*, (in press).
- 13 Prasad A V K, Kapil R S & Popli S P, *Indian J Chem*, **22B** (1983) 610.

# Synthesis of Pyrido[4,3-*b*]dibenzofuran, Pyrido[4,3-*b*]-phenoxathiin, 6-Ethylpyrido[4,3-*b*]phenothiazine & Related Compounds as Ellipticine Analogs†

DIBYENDU SENGUPTA‡ & NITYA ANAND\*

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226 001

Received 19 February 1982; revised and accepted 8 April 1985

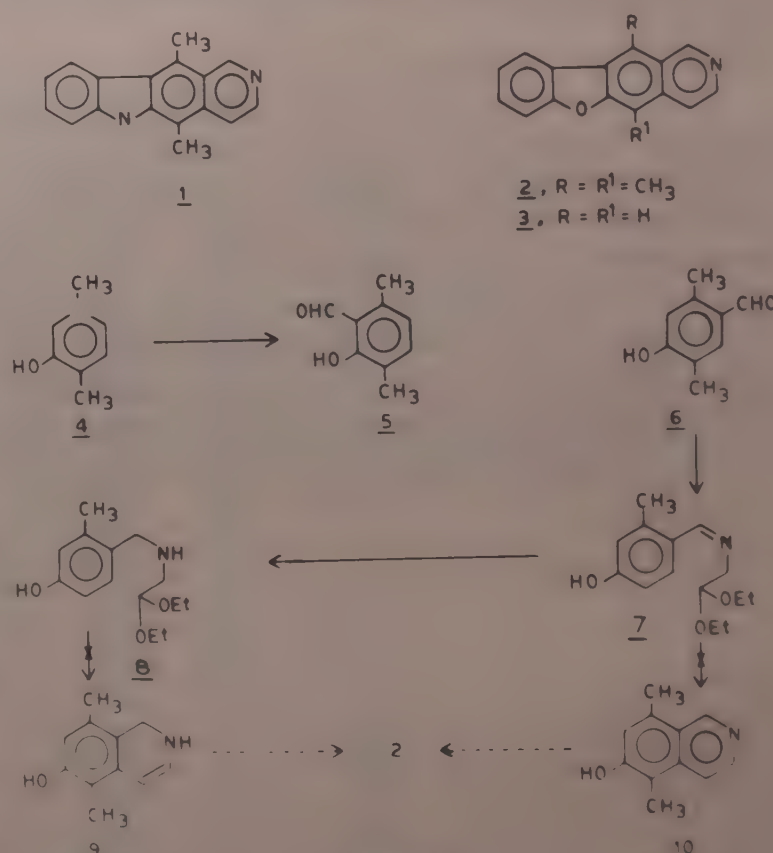
5,11-Dimethylpyrido[4,3-*b*]dibenzofuran (2), pyrido[4,3-*b*]dibenzofuran (3), pyrido[4,3-*b*]phenoxathiin (17) and 6-ethylpyrido[4,3-*b*]phenothiazine (18) have been synthesized as structural analogs of ellipticine. None of these compounds exhibits anticancer activity.

Ellipticine (1)<sup>1</sup> and a number of related pyridocarbazole alkaloids isolated from *Ochrosia elliptica* Labill and other *Ochrosia* species have been shown to possess marked anticancer activity against LE and PS tumor systems in experimental animals. However, in clinical practice these have limited utility on account of their poor oral absorption and some CNS side effects.

In an attempt to improve upon the biological activity of ellipticine it seemed rational to synthesise analogs in which the pyrrole ring is replaced by other heterocycles. Thus, the synthesis of 5,11-dimethylpyrido[4,3-*b*]dibenzofuran (2)<sup>2</sup>, pyrido[4,3-*b*]dibenzofuran (3), pyrido[4,3-*b*]phenoxathiin (17) and 6-ethylpyrido[4,3-*b*]phenothiazine (18) was carried out and the results are reported in this paper.

The synthesis of 2 and 3 was achieved by essentially following the route of Cromwell *et al.*<sup>3</sup> for the synthesis of ellipticine.

To synthesise 2,5,8-dimethyl-7-hydroxyl-1,2,3,4-tetrahydroisoquinoline (9) and 5,8-dimethyl-7-hydroxyisoquinoline (10) appeared to be the suitable starting materials. Reaction of 2,5-dimethylphenol (4) with Zn(CN)<sub>2</sub>-AlCl<sub>3</sub> in dry HCl gas (modified Gatterman reaction) gave 6-formyl-2,5-dimethylphenol (5)<sup>4</sup> and 4-formyl-2,5-dimethylphenol (6)<sup>4</sup> in 13 and 83% yields respectively. Condensation of 6 with aminoacetaldehyde diethyl acetal yielded the corresponding aminoacetal (7) which was reduced with NaBH<sub>4</sub> to the respective amine (8). Attempts to bring about cyclisation of 7 and 8 to 10 and 9 respectively using 70% H<sub>2</sub>SO<sub>4</sub>, PPA, 105% superphosphoric acid or HCOOH-HCHO as cyclisation agent remained unsuccessful (Scheme 1).

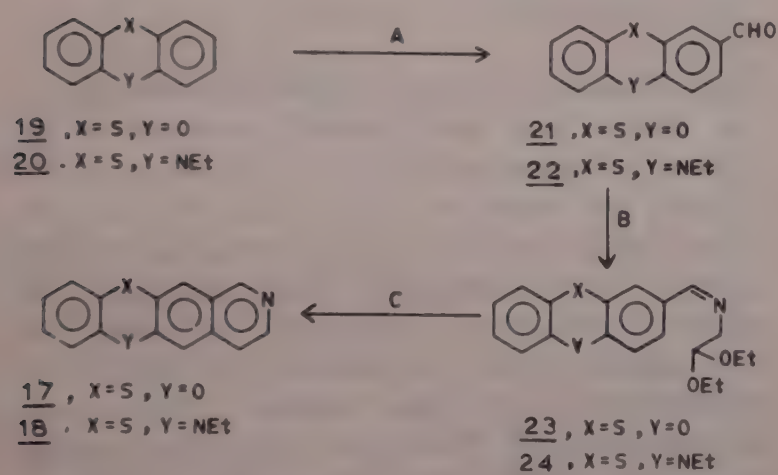
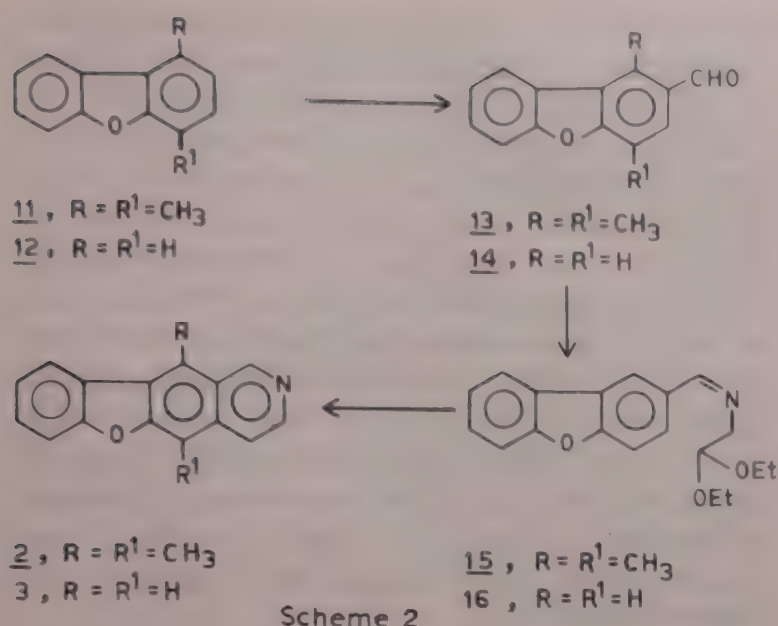


Scheme 1

In an alternative approach, formylation of 1,4-dimethyldibenzofuran (11)<sup>5</sup> by agents such as dimethylformamide-POCl<sub>3</sub>, N-methylformanilide-POCl<sub>3</sub> and zinc cyanide-AlCl<sub>3</sub>-HCl (dry) failed to yield the desired product 13. However, reaction of 11 with liquid HCN-HCl (gas)-AlCl<sub>3</sub> mixture yielded 6. The syntheses of 13 and 14 were carried out conveniently by treating 11 and 12 with butyl chloromethyl ether. Reaction of 13 and 14 with aminoacetaldehyde diethyl acetal gave the corresponding iminoacetals (15 and 16) which were subsequently cyclised to 5,11-dimethylpyrido[4,3-*b*]dibenzofuran (2) and pyrido[4,3-*b*]dibenzofuran (3) respectively using 105% superphosphoric acid (Scheme 2).

† CDRI Communication No. 2997

‡ Present address: Hindustan Insecticide Research Centre, Udyog Vihar, Gurgaon.



Reagents: A = SnCl<sub>4</sub>, Cl<sub>2</sub>CHO (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, dry CS<sub>2</sub> for **19**  
 = NMF-POCl<sub>3</sub>, *o*-dichlorobenzene for **20**  
 B = H<sub>2</sub>N-CH<sub>2</sub>-CH(OEt)<sub>2</sub>  
 C = 105% SPA

Phenoxathiin (**19**)<sup>7</sup> on treatment with butyl chloromethyl ether gave 2-formylphenoxathiin (**21**)<sup>8</sup> which underwent condensation with aminoacetaldehyde diethyl acetal to give the corresponding 2-(2,2-diethoxyethyliminomethyl)phenoxathiin (**23**). Cyclisation on **23** with 105% superphosphoric acid gave pyrido[4,3-*b*]phenoxathiin (**17**).

In an analogous manner 10-ethylphenothiazine (**20**) was treated with N-methylformanilide and POCl<sub>3</sub> to give 10-ethyl-3-formylphenothiazine (**22**) which on reaction with aminoacetaldehyde diethyl acetal gave the corresponding iminoacetals (**24**). Treatment of **24** with 105% superphosphoric acid for 30 min at 130-35° afforded 6-ethylpyrido[4,3-*b*]phenothiazine (**18**).

### Biological Activity

All the compounds were tested for their anticancer activity against WM, PS 238 and LE 1210 systems but none was found to be active.

### Experimental Procedure

All the melting points and boiling points are uncorrected. Melting points were determined on a Townson-Mercer melting point apparatus. IR Spectra were recorded on Perkin-Elmer 137 and 337 spectrophotometers ( $\nu_{\max}$  in cm<sup>-1</sup>), PMR spectra on a Varian A-60D instrument (chemical shifts in  $\delta$ , ppm) using TMS as internal standard, add mass spectra on a Hitachi RMU-6E single focussing spectrometer. TLC was carried out on silica gel G plates unless stated otherwise.

#### 2-Formyl-1,4-dimethyldibenzofuran (**13**)

To an ice cooled solution of 1,4-dimethyldibenzofuran (**11**)<sup>5</sup> (6.00 g, 0.03 mole) in dry methylene chloride (20 ml), was added, anhyd. stannic chloride (12.00 g, 5.32 mol) when the colour of the reaction mixture turned red. Thereafter dichloromethyl butyl ether (14 ml) was added to it dropwise under stirring. After the addition was over, the stirring was continued further for 45 min at room temperature and the reaction mixture poured over crushed ice. The organic layer was separated and the aqueous layer extracted with chloroform (3 × 100 ml). The chloroform extract was washed successively with 10% NaHCO<sub>3</sub> solution and ice cold water. The combined organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and solvent removed to give an oil which on trituration with hexane gave a yellow coloured solid, yield 3.5 g (58.3%), m.p. 110-12° (hexane), IR(KBr): 1700 (CHO); PMR(CDCl<sub>3</sub>): 2.35 and 2.72 (*d*, 6H, 2 × CH<sub>3</sub>, *J* = 22 Hz), 7.19-7.85 (*m*, 5H, Ar-*H*), 10.07 (*s*, 1H, CHO) (Found: C, 80.3; H, 5.6. C<sub>13</sub>H<sub>12</sub>O<sub>2</sub> requires C, 80.4; H, 5.4%).

Similarly, compound **14** was prepared from **12** in 84% yield m.p. 67-68°; IR(KBr): 1710 (CHO), PMR(CCl<sub>4</sub>): 6.90-8.04 (*m*, 9H, Ar-*H*), 9.75 (*s*, 1H, CHO), (Found: C, 79.9; H, 4.6, C<sub>13</sub>H<sub>8</sub>O<sub>2</sub> requires C, 79.6; H, 4.1%).

#### 2-(2,2-Diethoxyethyliminomethyl)-1,4-dimethyldibenzofuran (**15**)

A mixture of **13** (2.0 g, 0.09 mol) and aminoacetaldehyde diethyl acetal (1.7 g, 0.15 mol) was heated on a steam-bath for 30 min and dry benzene (100 ml) added to it. The reaction mixture was refluxed overnight using Dean-Stark water separator. The excess benzene was removed by distillation and the pale yellow oil on trituration with pet. ether (40-60°) gave **15** as a yellow solid, yield 3.0 g (99%), m.p. 60-62° (pet. ether 40-60°), IR(KBr): 1650 (HC=N), PMR(CDCl<sub>3</sub>): 1.24 [*t*, 6H, CH<sub>2</sub>CH(OCH<sub>2</sub>CH<sub>3</sub>), *J* = 7 Hz] 2.36 and 2.50 (*d*, 6H, CH<sub>3</sub>, *J* = 14 Hz), 6.92-7.95 (*m*, 6H, Ar-*H*), 8.62 (*s*, 1H, CH=N) (Found: C, 75.0; H, 7.5; N, 4.6. C<sub>21</sub>H<sub>25</sub>O<sub>3</sub>N requires C, 74.8; H, 7.3; N, 4.1%).

Using the above method, compound **16** was also

prepared, yield 7.50 g (78.1%); IR(neat): 1040 (HC = N), PMR(CDCl<sub>3</sub>): 1.19 [*t*, 6H, CH<sub>2</sub>CH(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, *J* = 7 Hz], 3.44-3.90 [*m*, 6H, CH<sub>2</sub>CH(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, *J* = 5 Hz], 7.24-8.10 (*m*, 6H, Ar - H) (Found: C, 72.9; H, 6.0; N, 4.0. C<sub>19</sub>H<sub>21</sub>O<sub>3</sub>N requires C, 73.3; H, 6.8; N, 4.5%).

#### 5,11-Dimethylpyrido[4,3-*b*]dibenzofuran (2)

To 105% superphosphoric acid (50 g) heated at 135-140° was added iminoacetal 15 (2.20 g, 0.068 mol), the reaction mixture stirred overnight, poured over crushed ice and the solid, thus separated, filtered off. The aqueous solution was neutralized with 10% NaOH and the turbid solution extracted with ethyl acetate (2 × 500 ml). The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and solvent removed to give 2 as a solid, yield 0.86 g (43.4%), m.p. 148-50° (benzene-pet. ether, 40-60°); IR(KBr): 1600, 808 (aromatic); PMR(CDCl<sub>3</sub>): 2.60 and 3.02 (*d*, 6H, 2 × CH<sub>3</sub>, *J* = 25 Hz); 7.34-9.60 (*m*, 7H, Ar - H).

Similarly, compound 3 was obtained from 16, yield 35% m.p. 186-88° (benzene), MS: *m/z* 219 (M<sup>+</sup>) (Found: C, 81.8; H, 4.5; N, 6.5. C<sub>15</sub>H<sub>9</sub>NO requires C, 82.1; H, 4.1; N, 6.0%).

#### 4-(2,2-Diethoxyethyliminomethyl)-2,5-dimethylphenol (7)

A mixture of 4-formyl-2,5-dimethylphenol (2.0 g, 0.15 mol) and aminoacetaldehyde diethyl acetal (1.6 g, 0.15 mol) was heated for 45 min on a boiling water-bath, dry benzene (10 ml) added to it and the reaction mixture refluxed overnight using Dean-Stark water separator. Solvent was removed from the reaction mixture to get a brown oil which was purified by chromatography over basic alumina using benzene as eluant, yield 1.8 g (81.8%); IR(neat): 1640 (HC = N) (Found: C, 66.5; H, 7.6; N, 4.5). C<sub>16</sub>H<sub>23</sub>O<sub>3</sub>N requires C, 66.9; H, 8.0; N, 4.8%).

#### 4-(2,2-Diethoxyethylaminomethyl)-2,5-dimethylphenol (8)

To a solution of 7 (6.0 g, 0.058 mol) in abs. methanol (50 ml), was added NaBH<sub>4</sub> (4.0 g, 0.105 mol) slowly and portionwise. The reaction mixture was stirred overnight at room temperature, neutralised with acetic acid and extracted with ethyl acetate (4 × 50 ml). The organic layer was separated, washed with 10% NaHCO<sub>3</sub> solution (2 × 50 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and solvent removed to give a yellow oil, which was chromatographed over basic alumina using 80-20% CHCl<sub>3</sub>-benzene as eluant to get the product as an oil, yield 5.2 g (86.6%); IR (neat): 3418 (Ar - CH<sub>2</sub> - NH) (Found: C, 66.8; H, 7.9; N, 5.5. C<sub>16</sub>H<sub>25</sub>O<sub>3</sub>N requires C, 61.4; H, 9.3; N, 5.3%).

#### 5-Ethyl-2-formylphenothiazine (22)

A solution of N-methylformamide (4.5 g, 0.21 mol) in anhyd. *o*-dichlorobenzene (20 ml) was cooled to 0°

and POCl<sub>3</sub> (5.25 g, 0.038 mol) was added to it dropwise at such a rate that temperature of the reaction mixture did not rise above 3°. 10-Ethylphenothiazine (20; 7.7 g, 0.033 mol) was then added and the reaction mixture heated on a water-bath for 4 hr, poured over crushed ice and saturated sodium acetals solution added to it. Thereafter, it was extracted with benzene (3 × 75 ml). The extract was washed with water (2 × 50 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), solvent removed and the residual oil steam-distilled to remove N-methylformamide and *o*-dichlorobenzene. The residue was extracted with benzene (3 × 75 ml), and the extract dried (Na<sub>2</sub>SO<sub>4</sub>) and solvent removed. The oil, thus obtained, solidified on keeping. It was filtered and crystallised from benzene, yield 6.5 g (84.4%), m.p. 90-92°; IR(KBr): 1690 (CHO); PMR(CDCl<sub>3</sub>): 1.4 (*t*, 3H, CH<sub>2</sub>-CH<sub>3</sub>, *J* = 7 Hz), 3.96 (*q*, 2H, CH<sub>2</sub>CH<sub>3</sub>, *J* = 7 Hz), 6.85-7.43 (*m*, 8H, Ar - H) (Found: C, 70.1; H, 4.9; N, 5.0. C<sub>15</sub>H<sub>12</sub>OSN requires C, 70.6; H, 5.1; N, 5.5%).

#### 2-(2,2-Diethoxyethyliminomethyl)phenoxathiin (23)

A mixture of phenoxathiin-2-aldehyde (4.5 g, 0.16 mol) and aminoacetaldehyde diethyl acetal (3.0 g, 0.16 mol) was heated on a steam-bath for 1 hr, dry benzene (100 ml) added to it and the reaction mixture refluxed using Dean-Stark water separator till separation of water was complete. The benzene was then evaporated and the resultant oil purified by chromatography over basic alumina column using benzene-hexane (50:50) as eluant to give 23 as a yellow thick oil, yield 4.0 g (70%); IR(neat): 1640 (HC = N); PMR(CDCl<sub>3</sub>): 1.23 [*t*, 6H, CH<sub>2</sub>CH(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, *J* = 7 Hz], 3.4-3.9 [*m*, 6H, CH<sub>2</sub>CH(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>], 4.82 [*t*, 1H, CH<sub>2</sub>CH(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, *J* = 6 Hz], 6.38-8.15 (*m*, 7H, Ar - H), 8.25 (*s*, 1H, CH = N) (Found: C, 64.6; H, 6.5; N, 4.3. C<sub>19</sub>H<sub>21</sub>NO<sub>3</sub>S requires C, 64.6; H, 6.3; N, 3.9%).

Similarly 24 was prepared from 22, yield 5.9 g (82%); IR(neat): 1640 (HC = N); PMR(CDCl<sub>3</sub>): 0.19-1.55 [*m*, 9H, CH(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> and NCH<sub>2</sub>CH<sub>3</sub>], 3.5-4.17 [*m*, 8H, CH<sub>2</sub>CH(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> and NCH<sub>2</sub>CH<sub>3</sub>], 4.84 [*t*, 1H, CH<sub>2</sub>-CH(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, *J* = 6 Hz], 6.82-7.59 (*m*, 7H, Ar - H), 8.2 (*s*, 1H, CH = N) (Found: C, 67.8; H, 4.2; N, 7.3. C<sub>21</sub>H<sub>26</sub>O<sub>2</sub>NS requires C, 68.1; H, 4.1; N, 7.6%).

#### Pyrido[4,3-*b*]phenoxathiin (17)

The iminoacetal 23 (2.0 g) Was added to 105% superphosphoric acid (50 g) at 135-40° during 3 min and the resulting dark red mixture stirred for 30 min, cooled, ice water (7 ml) added to it and the reaction mixture stirred overnight. The product was worked up as described above for 2, yield 125 mg (6%), m.p. 86-7°; MS: *m/z* 251 (M<sup>+</sup>); PMR(CDCl<sub>3</sub>): 7.00-8.58 (*m*, 9H, Ar - H) (Found: C, 71.3; H, 4.2; N, 5.1. C<sub>15</sub>H<sub>6</sub>OSN requires C, 71.7; H, 4.0; N, 5.6%).

Similarly, **18** was obtained from **24**, yield 105 mg (4%), m.p. 96°, MS:  $m/z$  278 ( $M^+$ ); PMR( $CDCl_3$ ): 1.45 ( $t$ , 3H,  $NCH_2CH_3$ ,  $J=7$  Hz), 4.1 ( $q$ , 2H,  $NCH_2-CH_3$ ,  $J=7$  Hz), 6.85-7.95 ( $m$ , 9H, Ar-H) (Found: C, 73.4; H, 5.0; N, 10.0.  $C_{17}H_{15}SN_2$  requires C, 73.0; H, 5.8; N, 10.1%).

#### Acknowledgement

The authors are thankful to the Cancer Chemotherapy Unit of this Institute for the evaluation of anticancer activity of the compounds. One of them (D S G) is thankful to the CSIR, New Delhi for the award of a junior research fellowship.

#### References

- 1 Ciebert B, *The alkaloids*, Vol. 8, edited by R H F Manske (Academic Press, New York) 1965, 335.
- 2 Fujiwara A N, Acton E M & Goodman L J, *Heterocyclic chemistry*, **6** (1969) 379.
- 3 Gramwell P A & Saxtan J E, *Chem Ind*, (1962) 45.
- 4 Clemo G R & Howarth H, *J Chem Soc*, (1929) 2376.
- 5 Trippett S, *J chem Soc*, (1957) 419.
- 6 Rieche A, Gross H & Hoft E, *chem Ber*, **93** (1960) 88.
- 7 Fuson R C & Cleveland E A, *Organic Synthesis*, Vol. II (John Wiley Sons Inc, New York) 1943, 485.
- 8 Vasilus G, Gioaba A & Maior D, *Chem Abstr*, **81** (1974) 47386S.

# Synthesis & Antibacterial Activity of 2-(1-Ethyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-alkoxyiminoacetic Acids & Their Esters†

D R SHRIDHAR\*, BHAGAT RAM, R R KRISHNA & V LAKSHMI NARAYANA

Chemistry Division, IDPL Research Centre, Indian Drugs and Pharmaceuticals Ltd, Hyderabad 500 037

Received 1 April 1985; accepted 3 July 1985

Various 1,4-dihydro-4-oxoquinolinylalkoxyimino acetic acids and their esters (V: 1-9) have been prepared by the reaction of the corresponding dihydroquinolineglyoxalic acid esters (III) either with hydroxylamine hydrochloride followed by O-alkylation or directly with methoxyamine hydrochloride. The intermediate glyoxalic acids (II), their esters (III) and the various geometrically isomeric oximinoacetic acid derivatives derived from them have been evaluated for their antibacterial activity.

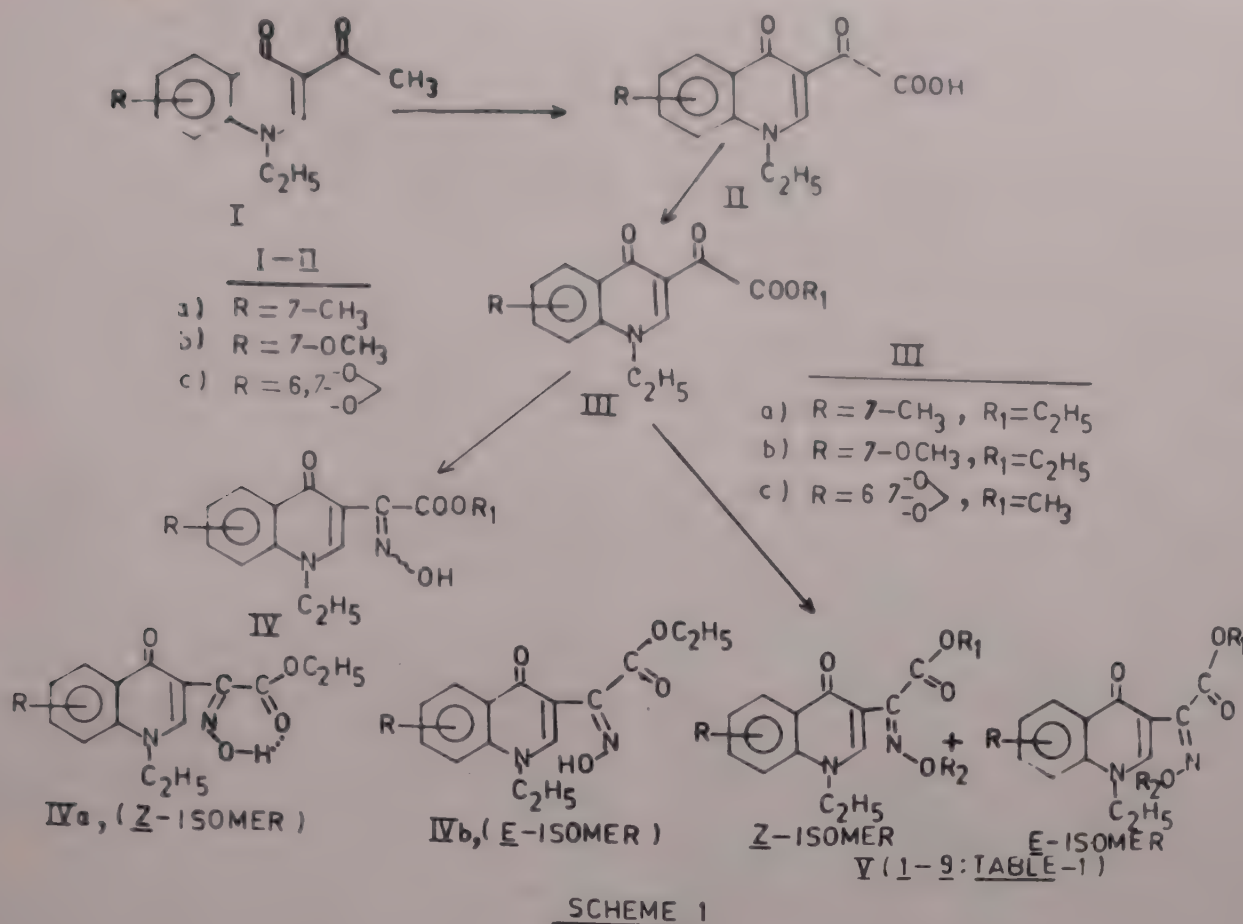
Ever since the discovery of nocardicins<sup>1</sup>, the synthesis of cephalosporins with an oximino ether function in the 7-acyl side chain has gained importance in order to find an antibiotic with an improved activity, especially against  $\beta$ -lactamase producing strains. Also naldixic acid and its analogs<sup>2</sup> are known to be good antibacterial agents against various gram negative

pathogens. With an aim to synthesise novel cephalosporins possessing both the oximino ether function and naldixic acid moiety in the 7-acyl side chain, we report herein the synthesis, configuration and the antibacterial activity of 2-(1-ethyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-alkoxyiminoacetic acids and their esters (V) (1-9, Table 1).

Table 1—Physical and Analytical Data of 1-9

Compound (configuration)	R <sub>2</sub>	m.p. (°C)	Mol. formula	N, % Found (calc.)*
R = 7-CH <sub>3</sub> ; R <sub>1</sub> = C <sub>2</sub> H <sub>5</sub>				
1a(Z)	C <sub>2</sub> H <sub>5</sub>	110-12	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	8.5 (8.5)
1b(E)	C <sub>2</sub> H <sub>5</sub>	98-99	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	9.0 (8.5)
2a(Z)	CH <sub>3</sub>	146-47	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub>	8.8 (8.9)
2b(E)	CH <sub>3</sub>	95-99	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub>	9.5 (8.9)
R = 7-OCH <sub>3</sub> ; R <sub>1</sub> = C <sub>2</sub> H <sub>5</sub>				
3a(Z)	C <sub>2</sub> H <sub>5</sub>	146	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub>	8.6 (8.1)
3b(E)	C <sub>2</sub> H <sub>5</sub>	156-57	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub>	8.3 (8.1)
4a(Z)	CH <sub>3</sub>	164-66	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub>	8.6 (8.4)
4a(E)	CH <sub>3</sub>	156-57	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub>	8.8 (8.4)
R = 6,7-Methylenedioxy; R <sub>1</sub> = CH <sub>3</sub>				
5a+b(Z+E)	CH <sub>3</sub>	138-40	C <sub>16</sub> H <sub>16</sub> N <sub>2</sub> O <sub>6</sub>	7.9 (8.4)
R = 7-CH <sub>3</sub> ; R <sub>1</sub> = H				
6a(Z)	C <sub>2</sub> H <sub>5</sub>	260-64	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	9.8 (9.3)
6b(E)	C <sub>2</sub> H <sub>5</sub>	250-52	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	9.4 (9.3)
7a(Z)	CH <sub>3</sub>	128-30	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub>	9.7 (9.7)
7b(E)	CH <sub>3</sub>	185-90	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub>	10.1 (9.7)
R = 7-OCH <sub>3</sub> ; R <sub>1</sub> = H				
8a(Z)	C <sub>2</sub> H <sub>5</sub>	180-83	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O <sub>5</sub>	8.6 (8.8)
8b(E)	C <sub>2</sub> H <sub>5</sub>	245-48	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O <sub>5</sub>	8.8 (8.8)
9a(Z)	CH <sub>3</sub>	148-50	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>5</sub>	9.3 (9.2)
9b(E)	CH <sub>3</sub>	226-28	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>5</sub>	9.5 (9.2)

\*Satisfactory C, H analyses have been obtained for all the compounds.



The desired compounds (1-9) were synthesised starting from 3-acetyl-1-ethyl-4-oxo-1,4-dihydroquinolines (Ia-c) which in turn were prepared following the known methods<sup>3</sup>. Selenium dioxide<sup>4</sup> oxidation of I in pyridine resulted in the corresponding glyoxalic acids (IIa-c). While IIa and IIb were obtained in 81% and 87% yields respectively, IIc was obtained in only 20% yield. The structures of IIa-c were in conformity with their <sup>1</sup>H and <sup>13</sup>C NMR spectra (see Experimental). Thus the <sup>13</sup>C NMR spectra of IIa and IIb showed signals for the carbonyl carbon atoms at 186.9, 173.6, 167.8 and 186.1, 174.6, 167.8 ppm respectively.

Attempts to prepare oximes of II by reaction with NH<sub>2</sub>OH.HCl under different conditions led to decarboxylation giving the corresponding nitriles. Hence, IIa-c were first esterified to the respective esters (IIIa-c) in excellent yields (80-90%). IIIa on refluxing with NH<sub>2</sub>OH.HCl in ethanol in the presence of NaOAc gave the oxime (IV) consisting of *syn*-(*Z*) and *anti*-(*E*) isomers (IVa and IVb) in 1:1 ratio, which could easily be separated by fractional crystallisation from dichloromethane/hexane. The structures of *Z* and *E* isomers were confirmed by their PMR spectra. The =N-OH proton in IVa and IVb appeared at  $\delta$  12.28 and 11.58 respectively. The downfield shift of 0.7 ppm in case of *syn*-isomer (IVa) can be attributed to the hydrogen bonding of =N-OH- with the adjacent -C=O group as shown in Scheme 1.

In addition to this, the observation that the alkaline hydrolysis of *anti*-isomer of the O-alkyloximino ester (V) proceeds with greater ease<sup>5</sup> as compared to that of *syn*-isomer further supports the above assigned structures for these compounds.

The oxime (IV: R=7-CH<sub>3</sub>), thus obtained, was alkylated with ethyl iodide in the presence of NaH/DMF or acetone/PEG-1000/K<sub>2</sub>CO<sub>3</sub> to give a mixture of V (1a and 1b) which was separated either by fractional crystallisation from DCM/hexane or by column chromatography over silica gel using benzene as the eluent. The isomers 1a and 1b were found to be identical (mp, mmp and IR) with those obtained by O-alkylation of the corresponding isomeric IVa and IVb (R=CH<sub>3</sub>). Pure *syn* and *anti*-isomers of oxime ethers (V) (2-4) were similarly prepared by the alkylation of IV (R=7-CH<sub>3</sub> or R=7-OCH<sub>3</sub>) with methyl and ethyl iodides.

O-Methyloximes (V) (2, 4 and 5) were also prepared directly by the reaction of corresponding III with CH<sub>3</sub>ONH<sub>2</sub>.HCl/NaOAc in refluxing ethanol. Separation of *syn* and *anti*-isomers of 2 and 4 was effected as described earlier. However, separation of *syn* and *anti*-isomers of 5 was not possible due to paucity of the material.

Saponification of the esters (1-4) with aq. KOH at 50-60° furnished the corresponding acids 6-9. It was observed that the hydrolysis of the *anti*-isomer was more facile than that of the *syn*-isomer. Taking the

advantage of this 1 was first reacted with half the quantity of KOH required to hydrolyse the total mixture at 50-60° for 3 hr whereby the *anti*-isomer V (1b) was completely hydrolysed (TLC) and was isolated from the aqueous layer. The residual unhydrolysed *syn*-isomer (1a) was then hydrolysed separately at 70-80° using excess KOH. The pure *syn* and *anti*-isomers of 6-9 were similarly prepared.

The structures of 1-9 were established on the basis of their elemental analyses and spectral data.

#### Antibacterial activity

Compounds (1-9) were tested *in vitro* for antibacterial activity against variety of gram +ve and gram -ve bacteria by serial dilution method as described earlier<sup>6</sup>. All the compounds were devoid of any antibacterial activity. However, the intermediate keto acids (IIa-c) showed moderate activity. IIa was effective against *Vibrio cholerae* and *Shigella dysenteriae* at 25 and 200 µg/ml respectively while IIb was active against these two organisms at 10 and 100 µg/ml, respectively. 6,7-Methylenedioxydihydroquinolinylglyoxalic acid (IIc) exhibited promising antibacterial activity *in vitro* against *Esch. coli*, *Sh. dysenteriae*, *V. cholerae* and *Salmonella typhi* by inhibiting their growth at 16, 24, 32 and 31 µg/ml respectively. Naldixic acid, the standard antibiotic used in the above antibacterial screening for comparative purposes inhibited the growth of the above four bacteria at 16, 8, 125 and 125 µg/ml, respectively.

#### Experimental Procedure

Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. IR spectra ( $\nu_{\max}$  in  $\text{cm}^{-1}$ ) were taken on a Perkin-Elmer 237 spectrophotometer; PMR spectra on a Varian EM-390 (90 MHz) or Jeol Fx-100 using TMS as internal reference; chemical shifts are expressed in  $\delta$ -scale (ppm). Microanalyses were performed using Hösli microcumbustion apparatus MK-101.

#### 1,4-Dihydro-1-ethyl-7-methyl-4-oxo-3-quinolineglyoxalic acid (IIa)

To a hot solution of acetylquinoline (Ia, 10.5 g, 0.046 mol) in dry pyridine (35 ml) was added selenium dioxide (7.5 g) in small portions. The reaction mixture was stirred at 60-70° for 5 hr, filtered, pyridine removed *in vacuo* and the residue diluted with cold water (100 ml). Traces of pyridine were removed by steam distillation, and the pH of the aqueous phase adjusted to 2.0 with 50% phosphoric acid. The separated solid, was filtered, suspended in cold water and basified to pH 8.0 with dil. NaOH. The solution

was washed with dichloromethane (2 × 50 ml), the acid regenerated with 50% phosphoric acid (pH 2.0), filtered, washed with cold water and dried to give 9.6 g (81%) of pure IIa as a colourless solid, m.p. 245° (d); IR(nujol): 1720 (COOH); 1650, 1610 (conjugated C=O); PMR (100 MHz, DMSO- $d_6$ ): 1.42 (t, 3H, N-CH<sub>2</sub>CH<sub>3</sub>), 4.42 (q, 2H, N-CH<sub>2</sub>CH<sub>3</sub>), 2.52 (s, 3H, CH<sub>3</sub>), 7.36 (d, 1H,  $J=9$  Hz, C<sub>6</sub>-H), 7.60 (s, 1H, C<sub>8</sub>-H), 8.18 (d, 1H,  $J=9$  Hz, C<sub>5</sub>-H), 8.80 (s, 1H, C<sub>2</sub>-H), <sup>13</sup>C NMR: 36.98, 37.80, 48.37, 113.4, 117.8, 125.9, 127.0, 138.9, 144.1, 148.6, 167.8, 173.6 and 186.9.

Compounds IIb [m.p. 235(d)] and IIc (>250) were prepared by the same procedure in 87% and 20% yields respectively.

#### Ethyl 1,4-dihydro-1-ethyl-7-methyl-4-oxo-3-quinolineglyoxalate (IIIa)

A solution of IIa (9.6 g, 0.037 mol) in ethyl alcohol (150 ml) containing catalytic amount of sulphuric acid (1.5 ml) was refluxed for 4 hr. It was concentrated under reduced pressure and diluted with cold water (200 ml). The solid which separated out was filtered, washed well with cold water and dried to give crude IIIa which was recrystallized from chloroform-hexane to give 9.5 g (89%) of pure IIIa, m.p. 161-63°; IR(nujol): 1720 (ester), 1640, 1620 (conjugated carbonyl); PMR (90 MHz, CDCl<sub>3</sub>): 1.33 (t, 3H, N-CH<sub>2</sub>CH<sub>3</sub>), 1.51 (t, 3H, COOCH<sub>2</sub>CH<sub>3</sub>), 4.27 (q, 2H, N-CH<sub>2</sub>), 4.42 (q, 2H, COOCH<sub>2</sub>CH<sub>3</sub>), 2.52 (s, 3H, CH<sub>3</sub>), 7.18-7.30 (m, 2H, C<sub>6</sub> & C<sub>8</sub>-H), 8.36 (d, 1H,  $J=9$  Hz, C<sub>5</sub>-H), 8.39 (s, 1H, C<sub>2</sub>-H) (Found: C, 66.8; H, 6.3; N, 5.1. C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub> requires C, 66.9; H, 5.9; N, 4.9%).

IIIb (m.p. 181-82°) and IIIc (250-52°) were similarly prepared from the corresponding acids in 90% and 80% yields respectively.

#### Ethyl 2-oximino-2-(1-ethyl-7-methyl-1,4-dihydro-4-oxo-quinolin-3-yl) acetate (IV; R=7-CH<sub>3</sub>)

To a solution of IIIa (3.46 g, 0.012 mol) in ethyl alcohol (200 ml), NH<sub>2</sub>OH.HCl (1.7 g) and anhydrous sodium acetate (2 g) were added and the mixture refluxed under stirring for 2 hr. After completion of reaction (TLC), solvent was removed under reduced pressure and the residual mass diluted with cold water (200 ml). The solid obtained was filtered, washed well with cold water and dried to give IV (3.5 g) as a mixture of (Z) and (E)-isomers (IVa and IVb), m.p. 184-85°.

The above mixture of oximes was dissolved in hot DCM (40 ml) and hexane (10 ml) was added to it when the Z-isomer (IVa) separated out in pure form which was filtered and dried to give 1.5 g of pure IVa (R=7-CH<sub>3</sub>) as colourless crystals, m.p. 189°; IR(nujol): 3130 (OH), 1730 (COOR), 1620, PMR (90 MHz, CDCl<sub>3</sub>):

1.2-1.6 (*m*, 6H, COOCH<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>CH<sub>3</sub>), 2.53 (*s*, 3H, CH<sub>3</sub>), 4.2-4.50 (*m*, 4H, COOCH<sub>2</sub>CH<sub>3</sub> & N-CH<sub>2</sub>CH<sub>3</sub>), 7.30 (*d*, 1H, *J*=9 Hz, C<sub>6</sub>-H), 7.63 (*s*, 1H, C<sub>8</sub>-H), 8.13 (*d*, 1H, *J*=9 Hz, C<sub>5</sub>-H), 8.53 (*s*, 1H, C<sub>2</sub>-H), 12.20 (*s*, 1H, =NOH) (Found: C, 63.0; H, 5.8; N, 9.5. C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub> requires C, 63.6; H, 6.0; N, 9.3%).

The mother liquor on concentration and cooling gave 1 g of a 1:1 mixture of IVa and IVb (R=7-CH<sub>3</sub>). Further concentration of the mother liquor followed by addition of hexane (10 ml) gave the pure *E*-isomer (IV, R=7-CH<sub>3</sub>) (1 g), m.p. 167-69°; PMR (90 MHz, CDCl<sub>3</sub>): 1.2-1.6 (*m*, 6H, COOCH<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>CH<sub>3</sub>), 2.53 (*s*, 3H, CH<sub>3</sub>), 4.2-4.60 (*m*, 4H, COOCH<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>CH<sub>3</sub>), 7.30 (*d*, 1H, *J*=9 Hz, C<sub>6</sub>-H), 7.63 (*s*, 1H, C<sub>8</sub>-H), 8.10 (*d*, 1H, *J*=9 Hz, C<sub>5</sub>-H), 8.37 (*s*, 1H, C<sub>2</sub>-H), 11.50 (*s*, 1H, =N-OH).

A mixture of oximes (IV, R=OCH<sub>3</sub>) was prepared similarly and the geometrical isomers separated by fractional crystallisation from ethyl alcohol-DCM mixture to give *Z* and *E*-isomers (IVa and IVb, R=OCH<sub>3</sub>) (m.p., yield): IVa (198-200°, 45%); IVb (190-91°, 40%).

*Ethyl 2-(1-ethyl-7-methyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-ethoxyiminoacetate (V; 1): Method-A*

To a slurry of sodium hydride (300 mg, 50%) in dry DMF (25 ml) at 10° was added IV (R=7-CH<sub>3</sub>) (1.5 g) in small portions. After stirring for 30 min at room temperature, a solution of ethyl iodide (2 ml) in DMF (50 ml) was added dropwise and the mixture heated at 60° for 3 hr. Removal of solvent under reduced pressure followed by dilution with cold water resulted in the separation of solid, which was filtered, washed well with cold water and dried to give 1 g of mixture of 1a and 1b.

*Method-B*

To a solution of IV (R=CH<sub>3</sub>) (1.5 g) in dry acetone (100 ml), PEG-1000 (1 g), K<sub>2</sub>CO<sub>3</sub> (3 g) and ethyl iodide (4 ml) were added and the mixture heated under reflux for 5 hr. Solvent was removed under reduced pressure and cold water (100 ml) added to the residue. The solid thus obtained was filtered, washed well with cold water and dried to give 1.1 g of a mixture of 1a and 1b; PMR (90 MHz, CDCl<sub>3</sub>): 1.2-1.6 (*m*, 9H, OCH<sub>2</sub>CH<sub>3</sub>, COOCH<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>CH<sub>3</sub>), 2.51 (*s*, 3H, CH<sub>3</sub>), 4.2-4.6 (*m*, 6H, OCH<sub>2</sub>CH<sub>3</sub>, and N-CH<sub>2</sub>CH<sub>3</sub>), 7.33 (*s*, 1H, C<sub>8</sub>-H), 7.23 (*d*, 1H, *J*=8 Hz, C<sub>6</sub>-H), 8.20 (*s*, 1H, C<sub>2</sub>-H of 1a), 8.10 (*s*, 1H, C<sub>2</sub>-H of 1b), 8.40 (*d*, 1H, *J*=8 Hz, C<sub>5</sub>-H).

Fractional crystallization of the above mixture from DCM-hexane afforded pure 1a (400 mg), m.p. 110-12° and 1b (300 mg), m.p. 98-99°. 1a was identical with the *syn*-isomer prepared separately by O-alkylation of

pure IVa (R=7-CH<sub>3</sub>) following exactly the method-B described above; IR (nujol): 1730, 1620; PMR (90 MHz, CDCl<sub>3</sub>): 1.2-1.6 (*m*, 9H, OCH<sub>2</sub>CH<sub>3</sub>, COOCH<sub>2</sub>CH<sub>3</sub>, N-CH<sub>2</sub>CH<sub>3</sub>), 2.51 (*s*, 3H, CH<sub>3</sub>), 4.15-4.6 (*m*, 6H, OCH<sub>2</sub>CH<sub>3</sub>, COOCH<sub>2</sub>CH<sub>3</sub>, N-CH<sub>2</sub>CH<sub>3</sub>), 7.30 (*d*, 1H, *J*=8 Hz, C<sub>6</sub>-H), 7.40 (*s*, 1H, C<sub>8</sub>-H), 8.25 (*s*, 1H, C<sub>2</sub>-H), 8.40 (*d*, 1H, *J*=8 Hz, C<sub>5</sub>-H) (Found: C, 65.3; H, 6.8; N, 8.5. C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> requires C, 65.5; H, 6.7; N, 8.5%).

Compounds (2-4) reported in Table 1 were synthesised similarly using ethyl iodide or methyl iodide for O-alkylation of IV (R=7-CH<sub>3</sub> or 7-OCH<sub>3</sub>).

*(Z)-2-(1-Ethyl-7-methyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-ethoxyimino-acetic acid (6a, Table 1)*

To a suspension of 1a (0.5 g, 0.0015 mol) in distilled water (10 ml) was added 1N NaOH (2 ml) and ethyl alcohol (0.5 ml). The mixture was heated at 70-80° with stirring for 6 hr. The aqueous solution was washed with DCM (2 × 25 ml) to remove any unreacted ester, cooled and acidified with 50% phosphoric acid to pH 2.0. The acid, thus separated, was filtered, washed well with cold water and dried to afford pure 6a (0.4 g), m.p. 260-64° (*d*); IR (nujol): 1740, 1620; PMR (90 MHz, CDCl<sub>3</sub>): 1.2-1.5 (*m*, 6H, OCH<sub>2</sub>CH<sub>3</sub>, N-CH<sub>2</sub>CH<sub>3</sub>), 2.51 (*s*, 3H, CH<sub>3</sub>), 4.1-4.4 (*m*, 4H, OCH<sub>2</sub>CH<sub>3</sub>, N-CH<sub>2</sub>CH<sub>3</sub>), 7.30 (*d*, 1H, *J*=9 Hz, C<sub>6</sub>-H), 7.66 (*s*, 1H, C<sub>8</sub>-H), 8.13 (*d*, 1H, *J*=9 Hz, C<sub>5</sub>-H), 8.37 (*s*, 1H, C<sub>2</sub>-H) (Found: C, 62.9; H, 5.8; N, 9.8. C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub> requires C, 63.6; H, 6.0; N, 9.3%).

*(E)-Isomer (6b, Table 1) was prepared as follows:*

To a suspension of 1b (0.5 g, 0.0015 mol) in distilled water (10 ml) was added 1N NaOH (2 ml) and ethyl alcohol (0.5 ml). The mixture was stirred at 50-60° for 4 hr and worked-up as above to give 6b (0.4 g), m.p. 250-52° (*d*); IR (nujol): 1730, 1620; PMR (90 MHz, DMSO-*d*<sub>6</sub>): 1.2-1.5 (*m*, 6H, OCH<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>CH<sub>3</sub>), 2.51 (*s*, 3H, CH<sub>3</sub>), 4.1-4.4 (*m*, 4H, OCH<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>CH<sub>3</sub>), 7.30 (*d*, 1H, *J*=9 Hz, C<sub>6</sub>-H), 7.66 (*s*, 1H, C<sub>8</sub>-H), 8.10 (*d*, 1H, *J*=9 Hz, C<sub>5</sub>-H), 8.33 (*s*, 1H, C<sub>2</sub>-H) (Found: C, 64.4; H, 6.4; N, 9.4. C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub> requires C, 63.6; H, 6.0; N, 9.3%).

*Hydrolysis of mixture of 1a and 1b*

To a mixture of 1 (1.08 g) in distilled water (10 ml) was added 1.016 N NaOH (1.52 ml) and ethyl alcohol (0.5 ml). The reaction mixture was heated at 50-60° for 4 hr, cooled, diluted with water (20 ml) and was extracted with DCM (3 × 50 ml). The aqueous layer was cooled, neutralised with 50% phosphoric acid to pH 2.0 and the acid that separated out was filtered, washed well with water and dried to give 0.4 g of pure 6b, m.p. 250-52° (*d*), identical with 6b obtained from 1b as described above.

The dichloromethane layer was concentrated to 5 ml and hexane (20 ml) added to collect 0.4 g of **1a** which was hydrolysed as above to get the pure **6a**, m.p. 260-64° (d), identical to **6a** prepared by the hydrolysis of **1a**.

*Ethyl 2-(1-ethyl-7-methyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-methoxyiminoacetate (2a, 2b; Table 1)*

A mixture containing **IIIa** (3 g, 0.01 mol), methoxyamino hydrochloride (1.32 g, 0.0158 mol) and sodium acetate (1.3 g, 0.0158 mol), ethyl alcohol (100 ml) and water (0.5 ml) was refluxed for 4 hr. The solvent was removed under reduced pressure, water (100 ml) added to it and the solid obtained filtered under suction. The crude solid was fractionally recrystallised from DCM-hexane to give 1.94 g of **2a**, m.p. 146-47° and 0.1 g of **2b**.

**2a**: IR (nujol): 1710, 1625; PMR (90 MHz, CDCl<sub>3</sub>): 1.32-1.58 (m, 6H, -OCH<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>CH<sub>3</sub>); 2.49 (s, 3H, 7-CH<sub>3</sub>); 3.95 (s, 3H, OCH<sub>3</sub>), 4.04-4.50 (m, 4H, -OCH<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>CH<sub>3</sub>), 7.20-7.29 (m, 2H, C<sub>6</sub>-H and C<sub>8</sub>-H), 8.10 (s, 1H, C<sub>2</sub>-H), 8.29 (d, 1H, J=10 Hz, C<sub>5</sub>-H) (Found: C, 64.5; H, 5.7; N, 8.8. C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub> requires C, 64.6; H, 6.3; N, 8.9%).

**2b**: IR (nujol): 1700, 1610; PMR (90 MHz, CDCl<sub>3</sub>): 1.29-1.52 (m, 6H, OCH<sub>2</sub>CH<sub>3</sub> and -N-CH<sub>2</sub>CH<sub>3</sub>), 2.51 (s, 3H, 7-CH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.34-4.42 (m, 4H, -OCH<sub>2</sub>CH<sub>3</sub> and -N-CH<sub>2</sub>CH<sub>3</sub>), 7.22-7.29 (m, 2H, C<sub>6</sub>-H and C<sub>8</sub>-H), 8.13 (s, 1H, C<sub>2</sub>-H), 8.29 (d, 1H, J=10 Hz, C<sub>5</sub>-H) (Found: C, 65.0; H, 6.1; N, 9.5. C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub> requires C, 64.6; H, 6.3; N, 8.9%).

Compounds (**4** and **5**) reported in Table 1 were also prepared by the above method.

### Acknowledgement

The authors thank Dr G S Reddi and his staff for antibacterial studies and the staff of the Analytical Laboratories of our Centre for spectral and elemental analyses. They also thank Prof Goverdhan Mehta, University of Hyderabad for PMR spectra.

### References

- 1 Kamiya T, *Recent advances in the chemistry of  $\beta$ -lactams antibiotics*, Special publication No. 28, edited by J Elks (The Chemical Society, London), 1977, 281.
- 2 (a) Leshner G Y, Froelich E J, Gruett M D, Bailey J H & Brundage R P, *J mednl Chem*, **5** (1962) 1063.  
(b) Gilis P M, Haemers A & Bollaeri W, *Eur J Chem-chim Ther*, **6** (1980) 499.
- 3 (a) Okumura K, Adachi T, Tomie M, Kondo K & Inoue I, *J chem Soc, Perkin-I*, (1972) 173.  
(b) Meszaros Z, Hermecz I, Somfai E, Horvath A & Vasvari L, *Brit Pat*, 1,505,427 (1978); *Chem Abstr*, **89** (1978) 109138q.  
(c) Albrecht A, *Prog Drug Res*, **21** (1977) 41.
- 4 Hatanake M & Ishimaru T, *J mednl Chem*, **16** (1973) 978.
- 5 (a) Cherry P C, Cook M C, Foxton M W, Gregson M, Gregory G I & Webb G B, *Recent advances in the chemistry of  $\beta$ -lactams antibiotics*, Special publication No. 28, edited by J Elks, (The Chemical Society, London), 1977, 145.  
(b) Euranto E K, *The Chemistry of carboxylic acids & esters*, edited by S Patai (John Wiley, New York), 1969, 522.
- 6 (a) Shridhar D R, Reddy Sastry C V, Vaidya N K, Reddy G S & Thapar G S, *J pharm Sci*, **65** (1976) 1074.  
(b) Shridhar D R, Reddy Sastry C V, Moorthy S R, Vaidya N K, Gopal Reddy P, Reddi G S & Thapar G S, *J mednl Chem*, **20** (1977) 149.

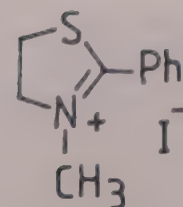
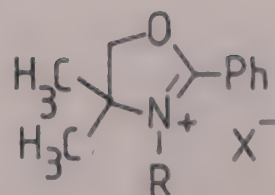
# Notes

## Heterocyclic Ring Interchange Reactions

HARJIT SINGH\* & RAKESH SARIN

Department of Chemistry, Guru Nanak Dev University,  
Amritsar 143 005

Received 3 July 1985; accepted 18 July 1985



	R	X
<u>1</u>	CH <sub>3</sub>	I
<u>2</u>	H	Cl

3

$\Delta^2$ -Oxazolinium and thiazolinium cations transfer their C(2) units to acyclic binucleophiles to furnish ring interchange non-aromatic heterocycles.

$\Delta^2$ -Oxazolinium and thiazolinium cations have been demonstrated to transfer their C(2) carbon fragment at carboxylic acid oxidation level to a variety of binucleophiles and form aromatic heterocyclic compounds<sup>1</sup>. The interchange of heterocyclic rings such as the transformation of dithiolanes to dioxolanes<sup>2,3</sup> and thiazolidines to oxazolidines<sup>4</sup> offers a variety of advantages in organic synthesis. The synthetic utility of azolines<sup>5,6</sup> led us to study the interchange behaviour of  $\Delta^2$ -azolines and consequently the carbon transfer character of azolinium cations to binucleophiles. This transformation is expected to yield heterocycles.

In a typical experiment, an equivalent amount of 1, 2-diaminoethane was added to a solution of 3, 4, 4-trimethyl-2-phenyl- $\Delta^2$ -oxazolinium iodide (**1**) in acetonitrile, when the yellow colour of **1** instantaneously disappeared and the resulting solution lacked the absorption at  $\lambda_{\max}$  350 nm of **1**. The reaction mixture after stirring for 2 hr was refluxed for another 2 hr. Usual work-up of the reaction mixture resulted in the isolation of 2-phenyl- $\Delta^2$ -imidazoline in 96% yield. Refluxing the reaction mixture immediately after

mixing the reactants, i.e. without stirring for 2 hr resulted in the formation of decomposition products.

Thus, **1**, 4, 4-dimethyl-2-phenyl- $\Delta^2$ -oxazolinium chloride (**2**) or 3-methyl-2-phenyl- $\Delta^2$ -thiazolinium iodide (**3**) reacted with 1,2-diaminoethane, 1,2-diaminopropane and 1,3-diaminopropane to furnish 2-phenyl- $\Delta^2$ -imidazoline, 4-methyl-2-phenyl- $\Delta^2$ -imidazoline and 2-phenyl-1,4,5,6-tetrahydropyrimidine respectively (see Table 1). Compound **1** or **2** on similar reaction with 2-aminoethanethiol furnished 2-phenyl- $\Delta^2$ -thiazoline, while **3** with 2-aminoethanol and 2-amino-2-methyl-1-propanol furnished 2-phenyl- $\Delta^2$ -oxazoline and 4,4-dimethyl-2-phenyl- $\Delta^2$ -oxazoline respectively. The reaction of **1** with 2-aminoethanol or 2-amino-2-methylpropan-1-ol resulted in products arising by oxazoline to oxazoline ring transformation. Likewise, **3** with 2-aminoethanethiol gave 2-phenyl- $\Delta^2$ -thiazoline (Table 1).

In conclusion, thiazolines as their quaternary salts can be transformed readily to oxazoline, imidazoline

Table 1—Reactions of Azolinium Cations (1-3) with Binucleophiles

Azolinium cations	Binucleophile	Product	Reaction time (hr) for			Product yield <sup>b</sup> (%) for		
			1	2	3	1	2	3
1/2/3	1,2-Diaminoethane	2-Phenyl- $\Delta^2$ -imidazoline	4	4	4	96	80	90
1/2/3	1,2-Diaminopropane	4-Methyl-2-phenyl- $\Delta^2$ -imidazoline	4	4	4	95	80	88
1/2/3	1,3-Diaminopropane	2-Phenyl-1,4,5,6-tetrahydropyrimidine	4	6	4	90	50	85
1/2/3	2-Aminoethanethiol hydrochloride <sup>a</sup>	2-Phenyl- $\Delta^2$ -thiazoline	10	10	8	15	10	40
1/2/3	2-Aminoethanol	2-Phenyl- $\Delta^2$ -oxazoline	8	10	6	50	30	70
1/2/3	2-Amino-2-methylpropan-1-ol	4,4-Dimethyl-2-phenyl- $\Delta^2$ -oxazoline	8		8	55		40

(a) An equivalent amount of triethylamine was used, and (b) imidazoline/pyrimidine derivatives isolated after extractive work-up were sufficiently pure but oxazolines and thiazolines were purified by chromatography.

and pyrimidine derivatives. Similarly oxazolines can be converted into imidazolines but interchange of oxazolines to thiazolines does not proceed smoothly.

We thank the CSIR, New Delhi, for financial assistance.

# References

1 Singh H & Sarin R, *Heterocycles*, **22** (1984) 1101.

2 Corey E J & Hase T, *Tetrahedron Lett.*, (1975) 3267.

3 Munavu R M & Szmant H H, *Tetrahedron Lett.*, (1975) 4543.

4 Ando W, Takata T, Huang L & Tamura Y, *Tetrahedron Lett.*, (1985) 869.

5 Reuman M & Meyers A I, *Tetrahedron*, **41** (1985) 837.

6 Stoit A R & Pandit U K, *Heterocycles*, **22** (1984) 1687; and references therein.

## Studies in Hydrazone Rearrangement: Synthesis of Anilides

VIDYA JOSHI\*, S S JALISATGI & M I HARI

Institute of Science, Madam Cama Road,  
Bombay 400 032

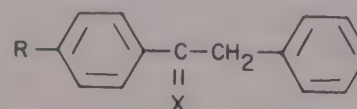
Received 21 September 1984; accepted 6 February 1985

Ketone tosylhydrazones (II) on diazotization with  $H_2SO_4$  and  $NaNO_2$  yield anilides (III).

The literature survey reveals that hydrazone rearrangement received little attention probably due to instability of hydrazones which are spontaneously converted into azines. We undertook the present work with a view to studying the scope and utility of hydrazone rearrangement in the synthesis of organic compounds.

A thorough search of literature shows that diazotization rearrangement of hydrazones of *meta*-substituted and *ortho*-disubstituted benzophenones,  $\alpha$ -phenylacetophenones and ketones containing heterocyclic radicals has not been reported as yet. Hence, we

chose *meta*- and disubstituted benzophenones (Ia and Ib), *para*-substituted deoxybenzoin (Ic-e) and 2-benzoylthiophene (If) as starting compounds. These ketones (Ia-f) were converted into tosylhydrazones (IIa-f), which on diazotization with  $H_2SO_4$  and  $NaNO_2$  gave anilides (IIIa-f; Table I). The structural assignments of III were based on elemental analyses and spectral data [IR(KBr): 3380-3300, 1555-1515,



Ic-e, IIc-e

Ic : R = H, X = O

Id : R =  $CH_3$ , X = O

Ie : R =  $-OCH_3$ , X = O

IIc : R = H, X =  $N-NH-SO_2C_6H_4-p-CH_3$

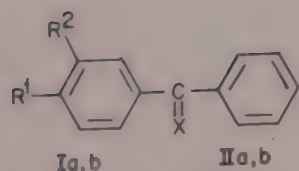
IId : R =  $CH_3$ , X =  $N-NH-SO_2C_6H_4-p-CH_3$

IIe : R =  $-OCH_3$ , X =  $N-NH-SO_2C_6H_4-p-CH_3$

Table I—Characterization Data of Tosylhydrazones (II) and Anilides (III)

Compd	m.p.* °C	Yield %	Eluent	Mol. formula	Found % (Calc.)		
					C	H	N
IIa	145(a)	43		$C_{21}H_{20}N_2O_2S$	68.8 (69.2)	5.5 5.5	7.8 7.7
IIb	180(b)	40		$C_{22}H_{22}N_2O_4S$	64.8 (64.4)	5.3 5.3	7.1 6.8
IIc	140(a)	43		$C_{21}H_{20}N_2O_2S$	69.1 (69.2)	5.3 5.5	3.9 3.8
IId	135(a)	60		$C_{22}H_{22}N_2O_2S$	69.5 (69.8)	5.6 5.8	7.2 7.4
IIe	147(c)	51		$C_{22}H_{22}N_2O_3S$	67.0 (67.0)	5.8 5.9	7.0 7.1
IIIf	158(a)	53		$C_{18}H_{16}N_2O_2S_2$	60.6 (60.7)	4.5 4.5	7.6 7.8
IIIa	124(d)	43	$C_6H_6$	$C_{14}H_{13}NO$	79.4 (79.6)	6.5 6.2	6.6 6.6
IIIb	154(a)	10	$C_6H_6$ -ether	$C_{15}H_{15}NO_3$	69.7 (70.0)	5.9 5.8	5.7 5.5
			(1:1)				
IIIc	117(e)	69	Ether- $CHCl_3$	$C_{14}H_{13}NO$	79.2 (79.6)	6.5 6.2	6.7 6.6
			(1:1)				
IIId	133(f)	69	$C_6H_6$ -ether	$C_{15}H_{16}NO$	80.3 (80.0)	6.9 6.6	6.1 6.2
			(4:1)				
IIIe	124(e)	65	$C_6H_6$ -ether	$C_{15}H_{15}NO_2$	74.2 (74.6)	6.4 6.2	5.8 5.8
			(4:1)				
IIIIf	145(e)	40	$C_6H_6$	$C_{11}H_9NOS$	64.9 (65.0)	4.3 4.4	6.9 6.9

\*Crystallized from (a) =  $C_6H_6$ -pet. ether (60-80°), (b)  $C_6H_6$ , (c) MeOH, (d) EtOAc-pet. ether (60-80°), (e) aq. EtOH and (f) EtOH.

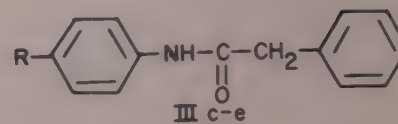


Ia :  $R^1 = H, R^2 = CH_3, X = O$

Ib :  $R^1 = R^2 = -OCH_3, X = O$

IIa :  $R^1 = H, R^2 = CH_3, X = N-NH-SO_2-C_6H_4-p-CH_3$

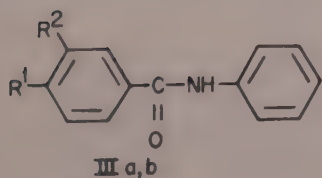
IIb :  $R^1 = R^2 = -OCH_3, X = N-NH-SO_2-C_6H_4-p-CH_3$



IIIc :  $R = H$

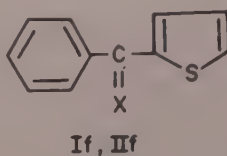
IIId :  $R = CH_3$

IIIe :  $R = -OCH_3$



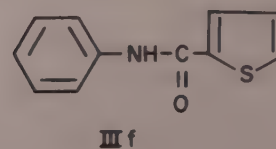
IIIa :  $R^1 = H, R^2 = CH_3$

IIIb :  $R^1 = R^2 = -OCH_3$



If :  $X = O$

IIIf :  $X = N-NH-SO_2-C_6H_4-p-CH_3$



1350-1255 (NH), 1681-1660  $cm^{-1}$  (C=O); and UV(MeOH): 211-217 (log  $\epsilon$  4.1-4.3) and 255-290 nm (log  $\epsilon$  4.3-4.1)].

The identity of IIIa-f was finally established by superimposable IR and m.m.p. determination with authentic specimens prepared by condensation of the corresponding amines with appropriate acid chlorides by Schotten-Baumann method. The IR(KBr) spectra of tosylhydrazones (IIa-f) exhibited absorption bands around 1350 and 1150  $cm^{-1}$  due to  $SO_2$  function.

The required ketones (Ia-f) were prepared by the methods described in literature<sup>1-5</sup>. Preparation of IIa-

f and their diazotization rearrangement to anilides (IIIa-f) were done according to the procedures described in our earlier article<sup>6</sup>.

We are thankful to Mrs J A Patankar and Mr D S More for elemental analyses.

#### References

- 1 Hartough H D & Kosak A I, *J Am chem Soc*, **69** (1947) 1012.
- 2 Ador E & Rilliet A A, *Ber dt chem Ges*, **12** (1879) 2298.
- 3 Allen C F H & Barker W E in *Organic synthesis*, Vol. XII (John Wiley, New York) 1932, 16.
- 4 Strassmann H, *Ber dt chem Ges*, **22** (1889) 1229.
- 5 Torres C, *Anales Soc espan fis quim*, **24** (1926) 82; *Chem Abstr*, **20** (1926) 2158.
- 6 Joshi V & Hari M I, *Indian J Chem*, **20B** (1981) 999.

## Structural Analogs of 2-Keto-3-deoxy-D-mannooctulosonic Acid

DIBYENDU SENGUPTA\*† & ROBERT CHERNIAK

Department of Chemistry

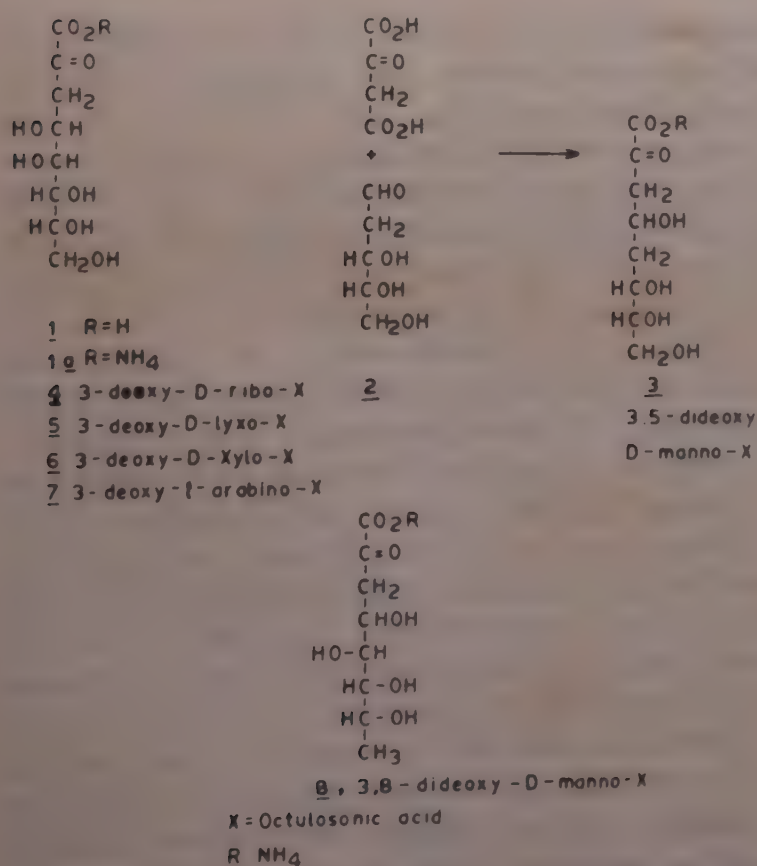
Georgia State University Atlanta Georgia 30303 USA

Received 2 February 1984; revised & accepted 8 April 1985

The synthesis of 3-deoxy sugars (4-8) has been carried out as structural analogs of 2-keto-3-deoxy-D-mannooctulosonic acid (KDO; 1).

2-Keto-3-deoxy-D-mannooctulosonic acid (KDO; 1) provides linkage between the complex polysaccharide antigen and lipid-A in the cell envelope of most of the gram negative bacteria.

As a prelude to the effect that analogs of KDO (1) have on the metabolism of 1, we have synthesised ammonium salt (1a) of 1 and 3,5-dideoxy-D-manno-(3), 3-deoxy-D-ribo- (4), 3-deoxy-D-lyxo- (5), 3-deoxy-D-xylo- (6), 3-deoxy-L-arabino- (7) and 3,8-dideoxy-D-manno- (8)octulosonic acids (Table 1; Scheme 1). The synthesis of first two compounds have already been reported in an earlier communication<sup>1,2</sup>.

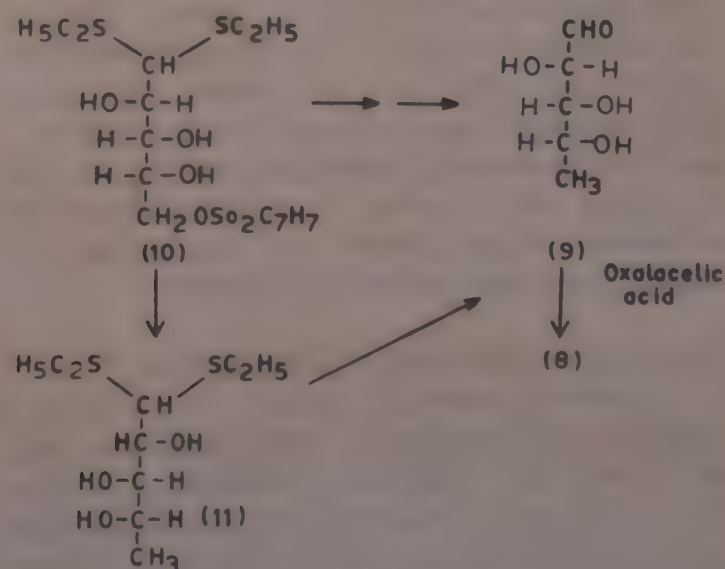


Compounds 4-7 were synthesised essentially following the method Ghalamboor *et al.*<sup>3</sup> as modified by Hershberger *et al.*<sup>4</sup> by the reaction of oxalacetic acid with respective peuloses at 23°C and pH 11 for 2 hr. The reaction mixture was purified by our modified procedure<sup>2</sup>. The material obtained in each case after lyophilisation was found to be highly hygroscopic. Attempts to convert them into ammonium or barium salt proved futile. Their *o*-acetyl derivatives were also hygroscopic. The compounds could, therefore, be characterised as 4-nitrophenylhydrozone derivatives which were very stable. The PMR spectra of the compounds could not be recorded due to their acute insolubility in common solvents.

5-Deoxy-D-arabinose (9) was prepared from 5-tosyl-1,1-diethylmercapto-D-arabinose (10) under the conditions essentially evolved by Levine and Compton<sup>4</sup> for the synthesis of monoacetone-D-arabinofuranoside. This method gave a mixture of D-arabinose and 5-deoxy-D-arabinose (15:85). The components of the mixture were converted into 1,1-diethylthio derivatives and separated by fractional crystallisation from ethanol-water (80:20).

Alternatively, compound 10 was reduced to 5-deoxy-1,1-diethylthio-D-arabinose (11) using 1.5 equiv. of LAH in dry ether. The resultant compound (11) was then heated with yellow mercuric oxide in 90% acetone to give 9 in 97% yield (Scheme 2). The purity of 9 was checked by paper chromatography in solvent-B (*R<sub>f</sub>* 0.58, lit.<sup>5</sup> *R<sub>f</sub>* 0.56).

Compound 9 was condensed with oxalacetic acid following the general procedure to give 3,8-dideoxy-1-mannooctulosonic acid (7) in 22% yield (Table 1).



\*Present address: Chemical Process Division, Central Drug Research Institute, Lucknow 226 001.

Table 1 – Characterization Data of Compounds 1a and 4-8 as Their 4-Nitrophenylhydrazine, Ammonium Salt and 4-Nitrophenylhydrazone Ammonium Salt Derivatives

Compd	Name	4-Nitrophenylhydrazone Ammonium salt				4-Nitrophenylhydrazone		Ammonium salt	
		Yield (%)	Mol. formula	N(%)		m.p. °C	R <sub>f</sub> (solvent)	IR	M <sup>+</sup> at m/z
				Found	Calc.				
1a	Ammonium-2-keto-3-deoxy-D-manno-octulosonate	18	C <sub>14</sub> H <sub>22</sub> N <sub>4</sub> O <sub>10</sub>	14.3	14.4	162-63	0.57(B) 0.61(C)	3100,1625,1405	255
3	Ammonium-2-keto-3,5-dideoxy-D-manno-octulosonate	17	C <sub>14</sub> H <sub>22</sub> N <sub>4</sub> O <sub>9</sub>	13.5	13.8	71-72	0.50(B) 0.57(C)	3100,1620,1410	239
4	Ammonium-2-keto-3-deoxy-D-ribo-octulosonate	18	C <sub>14</sub> H <sub>22</sub> N <sub>4</sub> O <sub>10</sub>	14.0	13.8	182-83	0.56(B) 0.58(C)	3100,1630,1410	255
5	Ammonium-2-keto-3-deoxy-D-lyxo-octulosonate	21	C <sub>14</sub> H <sub>22</sub> N <sub>4</sub> O <sub>10</sub>	14.0	13.8	139-40	0.57(B) 0.57(C)	3120,1640,1430	255
7	Ammonium-2-keto-3-deoxy-D-arabino-octulosonate	17	C <sub>14</sub> H <sub>22</sub> N <sub>4</sub> O <sub>10</sub>	14.4	13.8	70-72	0.52(B) 0.56(C)	3120,1625,1410	253
8	Ammonium 2-keto-3,8-dideoxy-D-manno-octulosonate	22	C <sub>14</sub> H <sub>22</sub> N <sub>4</sub> O <sub>9</sub>	14.0	14.4	152-53	0.64(B) 0.62(C)	3110, 1620, 1420	239

Solvents were concentrated under reduced pressure below 40°. TLC was performed on silica gel G or cellular layer. Paper chromatography was carried out on Whatman paper (45 × 57 cm PK brand). Electrophoresis was performed on Whatman paper using pyridine-AcOH-H<sub>2</sub>O (4:10:90) buffer at pH 6.4. Following solvent systems were used for TLC and paper chromatography: (A) benzene-acetone (55:45; v/v), (B) ethanol-pyridine-water-AcOH (5:5:1:2, v/v), (C) BuOH-pyridine-0.1N HCl (5:3:2; v/v), (D) EtOAc-pyridine-water-AcOH (5:5:4:1; v/v), and (E) butanol-pyridine-water (10:3:3; v/v). Column chromatography was carried out on fluorocil column using 1:2 ratio (w/w) between the product and packing material. IR spectra were recorded on a Perkin-Elmer 337 instrument. Melting points were determined on a Meltemp apparatus and are uncorrected.

#### Synthesis of KDO analogs: General method

A solution of oxalacetic acid (12.2 g, 92 mmol) in water (100 ml) was chilled to 5° and rapidly adjusted to pH 11 with 20% KOH and a solution of D-ribose (37.5 g, 250 mmol) in water (150 ml) immediately added to it. The mixture was allowed to stand at room temperature for 2 hr, and pH checked and readjusted to 11, if necessary, during this period. On the basis of

thiobarbituric assay (with KDO as standard) at different time intervals, the formation of 2-keto-3-deoxy-D-ribo-octulosonic acid was found to be complete after 2 hr and the amount of material formed was stoichiometric with the amount of oxalacetic acid used. The reaction mixture was adjusted to pH 5 with gl. acetic acid, diluted with water to 1 litre and applied to a column (6.5 × 10 cm) of Dowex 1.8 (HCO<sub>3</sub>) ion exchange resin (200-400 mesh). The column was washed with water till the eluate gave a negative test for arabinose by phenol-sulphonic acid procedure<sup>6</sup>. Compound 1 was then eluted with 0.5N ammonium hydrogen carbonate at a flow rate of 60 ml hr<sup>-1</sup>; 15 ml fractions were collected. Alternate fractions were analysed by ascending paper chromatography or by high voltage electrophoresis. Appropriate fractions were pooled, and the ammonium hydrogen carbonate was removed by reported lyophilisation or evaporation below 40°. The material from fractions 11-30 was homogeneous and identified as ammonium 3-deoxy-D-ribo-octulosonate by cochromatography with an authentic sample. Fractions 31-46 contained this ammonium salt and that of 3-carboxy derivative of 1, the latter being in larger amount. Fractions 47-61 contained traces of ammonium salt of 1, the 3-carboxy derivative and an unidentified product. The pure

product could not be crystallised as ammonium or barium salt. Its acetyl derivative was also hygroscopic.

The compound (100 mg) was treated with 4-nitrophenyl-hydrazin (100 mg) in ethanol-water (17:3), and the mixture heated on a leveling water bath for 5 min when all the material had dissolved. It was kept overnight in a refrigerator. The 4-nitrophenyl-hydrazone which crystallised out was filtered and recrystallised twice from ethanol-water (77:3). TLC in solvents B and C indicated it to be single component with traces of 4-nitrophenylhydrazine. The derivative was therefore purified by preparative TLC. The portion corresponding to 4-nitrophenylhydrazine of the ammonium salt of 1 was eluted with methanol and recrystallised from ethanol-water (17:3).

The results of other reactions are given in Table 1.

The authors are thankful to Prof. D W Boykin, Chairman for encouragement. One of them (D S G) is also thankful to the Georgia State University for the award of post doctoral fellowship (1975-1976).

#### References

- 1 Hershberger C, Davis M & Binkley S B, *J biol Chem*, **243** (1968) 1578.
- 2 Cherniak P, Jones R G & Sengupta D, *Carbohydrates Res*, **75** (1979) 39.
- 3 Chalembor L E M & Health E C, *J biol Chem*, **241** (1966) 3207.
- 4 Levine P A & Compton J, *J biol Chem*, **116** (1936) 189.
- 5 Levine P A & Shiter E T, *J biol Chem*, **106** (1934) 421.
- 6 Maurmayer R K, Livingston E M & Michaels R, *Mikrochim Acta*, (1956) 1600.

## Synthesis of Xambioona, a Bispyranoflavanone

A C JAIN\* & O D TYAGI

Department of Chemistry, University of Delhi, Delhi 110007

Received 10 June 1985; accepted 11 July 1985

Xambioona (4) has been synthesised by condensing 6-acetyl-5-hydroxy-2,2-dimethylchromene (2) and 6-formyl-2,2-dimethylchromene (1) in alkali followed by heterocyclisation of the resulting chalcone (3).

Xambioona was isolated by Pereira *et al.*<sup>1</sup> from the seeds of *Calopogonium mucunoides* along with three other new compounds. Its structure 2S-6'',6''',6''',6'''-tetramethylbispyrano(2'',3'':7,8; 2''', 3''':4',3')flavanone (4) was established on the basis of its PMR and mass spectral data and similarity of its CD curve with those of known natural compounds. Herein we provide synthetic support to structure (4) for this natural flavanone.

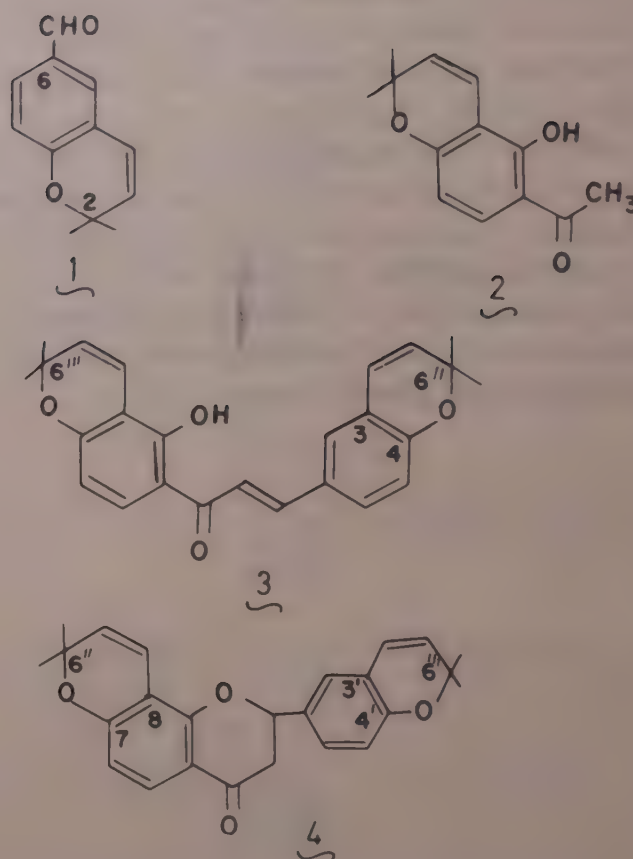
The key step involves condensation of 6-formyl-2,2-dimethylchromene (1) with 6-acetyl-5-hydroxy-2,2-dimethylchromene<sup>2</sup> (2) in the presence of methanolic potash followed by heterocyclization of the resulting chalcone (3) by refluxing its methanolic solution in the presence of anhydrous sodium acetate. The product was found to be identical with natural xambioona (4) in all respects (m.p., UV, IR and NMR).

### 4-(1,1-Dimethylpropargyloxy)benzaldehyde

Propargylation of 4-hydroxybenzaldehyde with 3-chloro-3-methyl-1-butyne followed by usual work-up afforded the desired product as a brown oil (1 g);  $R_f$  0.50 (benzene); IR: 2950, 1685 (C=O of -CHO); PMR: 1.73 (s, 6H,  $>C(CH_3)_2$ ), 2.67 (s, 1H,  $HC\equiv C-$ ), 7.31 (d,  $J = 10$  Hz, 2H,  $C_{3,5}-H$ ), 7.82 (d,  $J = 10$  Hz, 2H,  $C_{2,6}-H$ ), and 9.82 (s, 1H, -CHO).

### 6-Formyl-2,2-dimethylchromene (1)

The above aldehyde (1 g) was refluxed with N,N-dimethylaniline (50 ml) for 4 hr, cooled, poured into ice-cold water, acidified and extracted with ether. The ethereal solution after drying and evaporation afforded 1 as a brown oil (800 mg);  $R_f$  0.49 (benzene); IR: 1690 (C=O of -CHO), 1600; PMR: 1.38 (s, 6H,  $>C(CH_3)_2$ ), 5.60 (d,  $J = 10$  Hz, 1H,  $C_5-H$ ), 6.24 (d,  $J = 10$  Hz, 1H,  $C_6-H$ ), 6.12 (d,  $J = 10$  Hz, 1H,  $C_5-H$ ), 7.42 (dd,  $J = 10$  Hz,  $J = 2.5$  Hz, 1H,  $C_7-H$ ), 7.54 (d,  $J = 2.5$  Hz, 1H,  $C_8-H$ ) and 9.65 (s, 1H, -CHO).



### 2'-Hydroxy-6'',6''',6''',6'''-tetramethyl-bispyrano-(2'',3'':4,3; 2''',3''':4',3')chalcone (3)

A mixture of 6-acetoxy-5-hydroxy-2,2-dimethylchromene<sup>2</sup> (2) (220 mg, 1 mmol) and 1 (200 mg, 1.1 mmol) was kept in contact with methanolic KOH (280 mg/20 ml) at room temp for 3 days. The product crystallised from petrol to afford 3 as pale yellow needles (200 mg); m.p. 127-28° (lit.<sup>1</sup> m.p. 128°);  $R_f$  0.60 (petrol-benzene; 2:3).

### 6'',6''',6''',6'''-Tetramethyl-bispyrano-(2'',3'':7,8,2''',3'''; 4',3')flavanone (xambioona, 4)

A methanolic solution of 3 (200 mg) was warmed at 40-50° with anhydrous sodium acetate (800 mg) for 40 hr, poured into cold water and the solid collected. TLC showed it to be a mixture; hence it was separated by column chromatography. The product eluted from 70% benzene-petrol was crystallised from *n*-hexane to afford 4 as light yellow crystals (100 mg);  $R_f$  0.40 (benzene). It agreed with the description of natural compound, xambioona<sup>1</sup> in all respects (m.p., PMR, IR, UV).

One of us (O D T) is thankful to the CSIR, New Delhi for the award of a senior research fellowship.

### References

1. Pereira M O de S, Fantine F C & de Sousa J R, *Phytochemistry*, **21** (1982), 488.
2. Jain A C, Lal P & Seshadri T R, *Tetrahedron*, **26** (1970), 2631.

## Synthesis of Condensed Carbostyrils

T JAYACHANDRAN, R PARAMASIVAM & V T RAMAKRISHNAN\*

Department of Organic Chemistry, University of Madras,  
Madras 600 025

Received 20 September 1983; revised and accepted  
16 November 1985

3-Chloro-1-benzothiophene-2-carboxanilides (1) on treatment with aluminium chloride or under irradiation give [1]benzothieno[2,3-*c*]quinoline-6(5*H*)-ones (2).

As a part of our studies<sup>1-4</sup> on the synthesis of carbostyrils we wish to report here the synthesis of condensed carbostyrils incorporating a benzothiophene ring. 3-Chloro-1-benzothiophene-2-carboxanilides (1) were chosen as starting materials which on cyclisation could be expected to give carbostyrils (2) or

undergo Fries type reaction leading to condensed 4-quinolones or 1-indanones. However, we have observed that the amides (1) undergo simple cyclodehydrohalogenation both in the presence of anhyd.  $\text{AlCl}_3$  and on irradiation to give the carbostyrils (2).

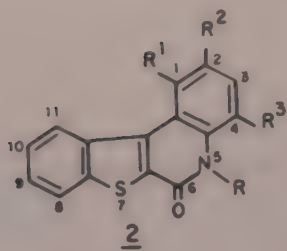
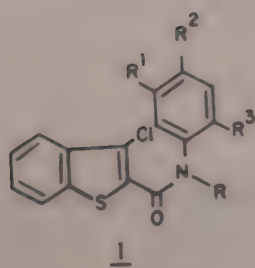
The anilides (1a-f; Table 1), prepared from 3-chloro-2-chloroformyl-1-benzothiophene and the respective anilines, were treated with anhyd. aluminium chloride in chlorobenzene at 95° to give [1]benzothieno[2,3-*c*]quinolin-6(5*H*)-ones (2a-f; Table 1). In order to arrive at structure 2, the quinolones 2c-e were converted into 6-chloro [1]benzothieno[2,3-*c*]quinolines (3a-c) by treatment with phosphorous oxychloride. The quinolone 2f however resisted the  $\text{POCl}_3$  treatment, obviously due to participation of the methoxy substituent which prevents the attack of

Table 1—Characterization Data of Anilides (1,4,5) and Condensed Carbostyrils (2,3)

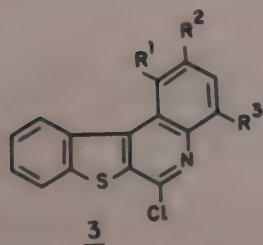
Compd	Yield* (%)	m.p., °C (Crystallised from)	Found (%) (Calc.)			PMR ( $\delta$ , ppm) (solvent)
			C	H	N	
1a	80	78-79 ( $\text{C}_6\text{H}_6$ -Hexane)	63.6 (63.7)	3.9 (4.0)	4.4 (4.6)	3.4 (s, 3H; N-CH <sub>3</sub> ) 7.0-8.0 (m, 9H, Ar-H) ( $\text{CCl}_4$ )
1b	74	81-82 ( $\text{C}_6\text{H}_6$ -Hexane)	64.7 (64.7)	4.3 (4.4)	4.8 (4.4)	1.2 (t, 3H, CH <sub>3</sub> ), 4.0 (q, 2H, CH <sub>2</sub> ) 7.0-7.8 (m, 9H, Ar-H) ( $\text{CCl}_4 + \text{CDCl}_3$ )
1c	75	168-69 (172) <sup>8</sup>	—	—	—	7.1-7.95 (m, Ar-H) ( $\text{CCl}_4 + \text{CDCl}_3$ )
1d	73	150-51 (EtOAc-Hexane)	63.8 (63.7)	4.1 (4.0)	4.9 (4.6)	1.83 (s, 3H, CH <sub>3</sub> ), 6.6-7.4 (m, 8H, Ar-H) (TFA)
1e	58	125-26 ( $\text{C}_6\text{H}_6$ -Hexane)	65.1 (64.7)	4.5 (4.5)	—	2.4 (s, 6H, 3 × CH <sub>3</sub> ), 6.95-8.0 (m, 7H, Ar-H), 8.85 (bs, NH) ( $\text{CCl}_4 + \text{CDCl}_3$ )
1f	70	146-47 (EtOAc-Hexane)	60.6 (60.5)	3.7 (3.8)	—	3.83 (s, 3H, OCH <sub>3</sub> ), 6.87-8.07 (m, 8H, Ar-H), 8.8 (bs, NH) ( $\text{CCl}_4 + \text{CDCl}_3$ )
2a	(89)	—	72.3 (72.5)	4.1 (4.2)	5.2 (5.3)	3.9 (s, 3H, N-CH <sub>3</sub> ), 7.3-8.8 (m, 8H, Ar-H) ( $\text{CCl}_4 + \text{CDCl}_3$ )
2b	82(89)	186-87 ( $\text{CHCl}_3$ -Hexane)	73.0 (73.2)	4.6 (4.7)	—	1.5 (t, 3H, CH <sub>3</sub> ), 4.58 (q, 2H, CH <sub>2</sub> ), 7.23-8.8 (m, 8H, Ar-H) ( $\text{CCl}_4$ )
2c	69(83)	> 290	—	—	—	—
2d	80(85)	> 300	—	—	—	—
2e†	(86)	244-45	—	—	—	—
2f	80(85)	> 290	—	—	—	—
3a	60	158-59	63.1 (63.1)	2.8 (2.8)	4.8 (4.9)	7.17-9.0 (m, Ar-H) ( $\text{CCl}_4 + \text{CDCl}_3$ )
3b	65	187-88	64.1 (64.1)	3.3 (3.3)	4.5 (4.7)	2.63 (s, 3H, CH <sub>3</sub> ), 7.17-8.83 (m, 7H, Ar-H) ( $\text{CDCl}_3$ )
3c	52	123-25	66.9 (67.0)	4.0 (4.1)	—	2.53 and 2.73 (2s, 6H, 2 × CH <sub>3</sub> ), 7.2-8.77 (m, 6H, Ar-H) ( $\text{CDCl}_3$ )
4	30	185-86	59.7 (59.5)	3.6 (3.6)	9.0 (9.3)	2.33 (s, 3H, CH <sub>3</sub> ), 7.17-8.33 (m, 7H, Ar-H), 9.5 (bs, NH) ( $\text{CDCl}_3 + \text{DMSO}-d_6$ )
5	55	119-121 (123-224) <sup>8</sup>	—	—	—	4.7 (d, 2H, benzylic CH <sub>2</sub> ), 7.13-7.83 (m, 10H, Ar-H and NH) ( $\text{CCl}_4 + \text{CDCl}_3$ )

\*Figures in parentheses correspond to the yields obtained by irradiation method

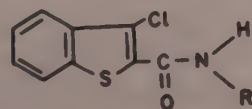
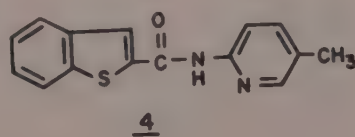
† $m/z$  279 ( $\text{M}^+$ ).



	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
a.	CH <sub>3</sub>	H	H	H
b.	C <sub>2</sub> H <sub>5</sub>	H	H	H
c.	H	H	H	H
d.	H	H	CH <sub>3</sub>	H
e.	H	CH <sub>3</sub>	H	CH <sub>3</sub>
f.	H	H	OCH <sub>3</sub>	H



	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
a.	H	H	H
b.	H	CH <sub>3</sub>	H
c.	CH <sub>3</sub>	H	CH <sub>3</sub>



5: R = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>

6: R = H

POCl<sub>3</sub> on the amide carbonyl. The formation of 2 from 1 in the presence of AlCl<sub>3</sub> may be regarded as intramolecular Friedel-Crafts cyclization.

The irradiation of 1 which was carried out in chloroform solution under nitrogen atmosphere<sup>5</sup>, gave 2 in almost quantitative yields. The light-induced cyclodehydrohalogenation was found to be so facile that the N-alkylanilides (1a, b) underwent cyclisation to some extent even in ordinary day light as detected by TLC. In any case, no product derived from photo-Fries type of reaction was detected.

With a view to extending our studies to related ring systems, N-(5'-methyl-2-pyridyl)-1-benzothiophene-2-carboxamide (4) was prepared which however did not undergo cyclisation in the presence of AlCl<sub>3</sub> or on irradiation. N-benzyl-3-chloro-1-benzothiophene-2-carboxamide (5) gave only 3-chloro-1-benzothiophene-2-carboxamide (6) on reaction with aluminium chloride but remained unreactive on irradiation. Formation of the stable benzyl cation probably favoured the cleavage of the nitrogen-benzyl bond in 5 to give 6. The deactivating effect of the pyridine ring system is probably the reason for the recovery of the amide 4.

Melting points are uncorrected. Following instruments were used: Beckmann IR 20 for IR

spectra; Hitachi Perkin-Elmer RMU-6E and Varian MS-30 for mass spectra; Varian A-60 and T-60, and Perkin-Elmer R-32 for PMR spectra with TMS as internal standard.

### 3-Chloro-N-ethyl-1-benzothiophene-2-carboxanilide (1b)

3-Chloro-2-chloroformyl-1-benzothiophene was prepared by the reported procedure<sup>6</sup> involving treatment of cinnamic acid (14.8 g, 0.1 mol) with excess thionyl chloride (48.0 g, 0.2 mol) in the presence of a catalytic amount of pyridine (1 ml). The mixture was poured into hexane and the hexane solution cooled to get the desired acid chloride as a solid (9.0 g, 40%), m.p. 113-14° (lit.<sup>6</sup>, m.p. 114-15°).

The above acid chloride (4.6 g, 20 mmol) in dry benzene was added dropwise to N-ethylaniline (2.48 g, 20 mmol) in dry benzene (50 ml) in the presence of pyridine (2.5 ml) and the mixture stirred for 15 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with dil. HCl, sodium hydrogen carbonate and water, dried (MgSO<sub>4</sub>) and solvent removed. The residue was purified by crystallisation from benzene-pet. ether (60-80°) to get 1b (4.19 g, 74%); IR: 1630 cm<sup>-1</sup> (amide C=O); MS: *m/z* 315(317) (M<sup>+</sup>), 280, 195(197), 167(169), 132, 123(125), 91, 77.

All the other anilides were prepared likewise and their characterization data are given in Table 1.

### Reaction of 1b with aluminium chloride: Formation of N-ethyl[1]benzothieno[2,3-c]quinolin-6(5H)-one (2b)

A mixture of 1b (2.0 g) and anhyd. aluminium chloride (6.0 g) in chlorobenzene (25 ml) was heated on a steam-bath for 2 hr. The mixture was poured onto ice-dil. HCl and extracted with chloroform. The organic layer was washed with water, dried (MgSO<sub>4</sub>), solvent removed and the residue chromatographed over a silica gel column. Elution with benzene furnished 2b (1.52 g, 82%), m.p. 186-87 (CHCl<sub>3</sub>-hexane); IR = 1630 cm<sup>-1</sup> (amide C=O); MS: *m/z* 279 (M<sup>+</sup>), 251, 223, 222, 207.

Other anilides (1) on similar treatment with AlCl<sub>3</sub> furnished the respective quinolones (2), the characterization data of which are given in Table 1. The mass spectrum of 2a exhibited significant peaks at *m/z* 265 (M<sup>+</sup>), 236, 218, 208. The amide 4 (2.0 g) was recovered quantitatively even after heating for 12 hr with AlCl<sub>3</sub> on a steam-bath. On the other hand, the N-benzylamide 5 (1.0 g) on treatment with AlCl<sub>3</sub> in chlorobenzene at 95° gave 3-chloro-1-benzothiophene-2-carboxamide (6) (0.17 g, 20%), m.p. 240-42° (lit.<sup>7</sup>, 235-37); IR = 1625 (amide C=O), 3360 cm<sup>-1</sup> (amide NH); MS: *m/z* 211(213), (M<sup>+</sup>), 195(197), 167(169).

The difficult to characterise quinolones (**2**) were heated with  $\text{POCl}_3$  on a steam-bath for 2 hrs. The mixture was poured onto ice and extracted with chloroform. The organic layer, after washing with water, drying and concentration, gave a residue which was purified by passing through a silica gel column. The quinolones **2c**, **d** and **e**, were characterized as 6-chloro-[1]-benzothieno[2,3-c]quinolines (**3a-c**). Their characterization data are given in Table 1. The mass spectrum of **3c** exhibited significant peaks at  $m/z$  297(299) ( $\text{M}^+$ ), 282(284), 262, 246, 234, 147, 129, 104, 103. The quinolone **2f** was recovered unchanged even after refluxing with  $\text{POCl}_3$  for 12 hr.

#### *Irradiation of 1b: Formation of 2b*

A solution of **1b** (1.0 g) in dry chloroform (100 ml) was taken in a quartz vessel, flushed with nitrogen and irradiated in a Rayonet Photochemical reactor equipped with eight RUL 208 lamps of 254 nm wavelength. After 8 hr of irradiation, the solution was concentrated to get the quinolone **2b** (0.78 g, 89%), identified by direct comparison (m.m.p., IR, PMR) with that obtained from **1b** and  $\text{AlCl}_3$ . A similar irradiation of N-methylanilide **1a** (1.0 g) gave the quinolone **2a** (0.78 g, 89%). The other anilides (**1c-f**) on irradiation (254 nm) in chloroform solution deposited

the respective quinolones (**2c-f**) on the walls of the reaction vessel. The high melting quinolones were identified by comparison of their IR spectra with those of the respective  $\text{AlCl}_3$  reaction products. The irradiation (254 nm) of **4** and **5** in chloroform solution for 30 hr under nitrogen atmosphere did not give any product and only the starting materials were recovered.

We thank Professors Walter Lwowski and J H Boyer for mass spectra and Dr R Balasubramanian for microanalysis. We are grateful to Professor S Swaminathan for facilities and the UGC, New Delhi for financial assistance.

#### References

- 1 Manimaran T, Thiruvengadam T K & Ramakrishnan V T, *Synthesis*, (1975) 739.
- 2 Manimaran T & Ramakrishnan V T, *Indian J Chem*, **18B** (1979) 324.
- 3 Manimaran T & Ramakrishnan V T, *Indian J Chem*, **18B** (1979) 78.
- 4 Natarajan M, Manimaran T & Ramakrishnan V T, *Indian J Chem*, **23B** (1984) 529.
- 5 In the course of our work a parallel report appeared: Kano S, Ozaki T & Hibine S, *Heterocycles*, **12** (1979) 489.
- 6 Higa T & Krubsack A J, *J org Chem*, **40** (1975) 3037.
- 7 Wright W B & Brabander H I, *J heterocycle chem*, **8** (1971) 711.
- 8 Moll R & Hesse B, *Z Chem*, **17** (1977) 133.

## Regiochemistry of Alkylation in Substituted 1,2,4-Triazoles<sup>a,b</sup>

R B MITRA\*, Z MULJIANI, A M PADHYE & S R DESHPANDE

National Chemical Laboratory, Pune 411 008

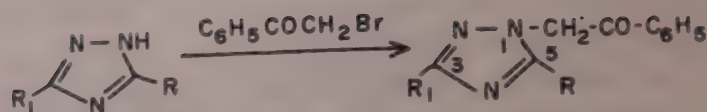
Received 5 July 1984; accepted 13 May 1985

The regiochemistry of N-alkylation of substituted 1, 2, 4-triazoles has been studied and the results indicate that steric factors play a significant role in determining the site of N-alkylation in these compounds.

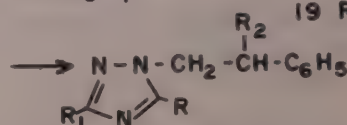
Derivatives of 1, 2, 4-triazole are of intense current interest in view of the wide ranging biological activity exhibited by these compounds as drugs<sup>1</sup>, fungicides<sup>2</sup> and plant growth regulators<sup>2</sup>. As a part of our programme in preparing some novel fused systems containing the 1, 2, 4-triazole unit, it became necessary to assign unambiguous structures to the major products obtained on phenacylation of substituted 1,2,4-triazoles (1-4)<sup>3</sup>.

A perusal of literature showed that not much attention has been paid to the study of regiochemistry of N-alkylation in substituted triazoles, although it has been established<sup>4,5</sup> that alkylation takes place preferentially at the N<sub>1</sub> or N<sub>2</sub> position; the N<sub>4</sub> derivatives are either not formed at all or obtained in very low yields<sup>6</sup>.

We have assigned structures to our phenacylated products in the following manner. Triazole (1) was reacted with phenacyl bromide in acetone and potassium carbonate at 0-10°. PMR<sup>c</sup> of the crude product (90%) showed essentially a single major compound which was crystallised from CCl<sub>4</sub>-CHCl<sub>3</sub> to give a sharp melting (m.p. 116°) compound which was assigned structure (5)<sup>d</sup> by X-ray crystallography; PMR: 1.23 (3H, *t*, *J* = 8Hz), 4.33 (2H, *q*, *J* = 8Hz), 5.73 (2H, *s*), 7.56 (3H, *m*), 8.0 (2H, *dd*, *J* = 6, 2Hz), 8.36 (1H, *s*). Compound (5) was reduced with LAH in THF to give the diol (6), m.p. 118° (85%), which on treatment with thionyl chloride in chloroform in the cold gave the dichloro compound (7) as a crystalline solid, m.p. 82-



- |  |  |
|--|--|
| 1 R = H, R <sub>1</sub> = COOC <sub>2</sub> H <sub>5</sub> | 5 R = H, R <sub>1</sub> = COOC <sub>2</sub> H <sub>5</sub> |
| 2 R = CH <sub>3</sub> , R <sub>1</sub> = SCH <sub>3</sub>  | 10 R = CH <sub>3</sub> , R <sub>1</sub> = SCH <sub>3</sub> |
| 3 R = H, R <sub>1</sub> = CH <sub>3</sub>                  | 15a R = CH <sub>3</sub> , R <sub>1</sub> = H               |
| 4 R = CH <sub>3</sub> , R <sub>1</sub> = Br                | 15b R = H, R <sub>1</sub> = CH <sub>3</sub>                |
|  | 19 R = CH <sub>3</sub> , R <sub>1</sub> = Br               |



- |   |
|---|
| 6 R = H, R <sub>1</sub> = CH <sub>2</sub> OH, R <sub>2</sub> = OH                 |
| 7 R = H, R <sub>1</sub> = CH <sub>2</sub> Cl, R <sub>2</sub> = Cl                 |
| 8 R = H, R <sub>1</sub> = CH <sub>2</sub> SPh, R <sub>2</sub> = SPh               |
| 9 R = H, R <sub>1</sub> = CH <sub>3</sub> , R <sub>2</sub> = H                    |
| 11 R = -CH <sub>3</sub> , R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = OH |
| 12 R = -CH <sub>3</sub> , R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = Cl |
| 13 R = CH <sub>3</sub> , R <sub>1</sub> = SCH <sub>3</sub> , R <sub>2</sub> = SPh |
| 14 R = CH <sub>3</sub> , R <sub>1</sub> = H, R <sub>2</sub> = H                   |
| 16a R = CH <sub>3</sub> , R <sub>1</sub> = H, R <sub>2</sub> = OH                 |
| 16b R = H, R <sub>1</sub> = CH <sub>3</sub> , R <sub>2</sub> = OH                 |
| 17a R = CH <sub>3</sub> , R <sub>1</sub> = H, R <sub>2</sub> = Cl                 |
| 17b R = H, R <sub>1</sub> = CH <sub>3</sub> , R <sub>2</sub> = Cl                 |
| 18a R = CH <sub>3</sub> , R <sub>1</sub> = H, R <sub>2</sub> = SPh                |
| 18b R = H, R <sub>1</sub> = CH <sub>3</sub> , R <sub>2</sub> = SPh                |

83° (76%). The dithiophenyl derivative (8) was obtained as a thick oil (65%) by refluxing 7 with sodium thiophenate in ethanol for 4 hr. Desulphurisation of 8 with Raney nickel, in acetone-ethanol (9:1) at room temperature for 12 hr resulted in the formation of the phenethyl derivative (9) as a colourless oil (86%); PMR: 2.41 (3H, *s*), 3.13 (2H, *t*), 4.28 (2H, *t*), 7.15 (5H, *m*), 7.63 (1H, *s*).

Triazole (2) was treated with phenacyl bromide as above. PMR of the crude product (90%) showed a major isomer (80%) which was crystallised from benzene-pet. ether to give a sharp melting (102°) crystalline compound; PMR: 2.36 (3H, *s*), 2.56 (3H, *s*), 5.6 (2H, *s*), 7.53 (3H, *m*), 7.9 (2H, *dd*, *J* = 6, 2Hz). This compound was identified as 10 in the following way. Sodium borohydride reduction of 10 gave the alcohol (11) as a crystalline compound, m.p. 122° (90%), which was converted into the chloro compound (12) (oil, 98%), 13 (oil, 86%) and finally to the phenethyl derivative (14) have the following PMR: 1.96 (3H, *s*), 3.11 (2H, *t*), 4.26 (2H, *t*), 7.15 (5H, *m*), 7.82 (1H, *s*). Because of the difference in chemical shifts of methyl and heteroaromatic protons in 9 and 14, compound (14) can have the structure indicated or it can be the less

(a) Presented at National Symposium on Heterocyclic Chemistry, Jaipur, 5-8 Feb. 1985.

(b) NCL Communication No. 3551.

(c) PMR spectra were recorded in CDCl<sub>3</sub> on WH-90 FT Spectrometer. Chemical shifts are given in  $\delta$  values. Where not described all compounds gave satisfactory NMR spectra.

(d) All new compounds were subjected to mass spectra and/or elemental analyses.

likely N<sub>4</sub>-substituted isomer. The possibility of its being the N<sub>4</sub>-isomer was ruled out by preparing authentic 3-methyl-4-phenethyl-1, 2, 4-triazole by an unambiguous route<sup>7</sup> as follows: Reaction of 4-phenethyl-3-thiosemicarbazide with ethyl *ortho* acetate resulted in 4-phenethyl-3-methyl-5-mercepto-1, 2, 4-triazole which was desulphurised after conversion to the *-s*-CH<sub>3</sub> derivative to give 3-methyl-4-phenethyl-1, 2, 4-triazole<sup>3</sup>. The N<sub>4</sub>-isomer could be distinguished from **9** and **14** by its PMR [2.11 (3H, *s*), 2.95 (2H, *t*), 4.17 (2H, *t*), 7.24 (5H, *m*), 7.88 (1H, *s*)], thus confirming the structure (**14**) as indicated.

The total crude product (90%) obtained as a semisolid by reacting **3** with phenacyl bromide displayed PMR signals at 2.41, 2.43 (3H, *s*), 5.6 (2H, *s*), 7.6 (3H, *m*), 7.86 (0.4H, *s*), 8.0 (2H, *dd*, *J* = 6, 2Hz), 8.13 (0.6H, *s*). Comparison of the methyl and heteroaromatic proton signals showed it to be an approximately 40:60 mixture of **15a** and **15b** which was further confirmed by the conversion described above. Compound (**15**) was converted into a mixture of alcohols (**16a**) and (**16b**) (98%), chloro compounds (**17a**) and (**17b**) (95%) and phenylthio compounds (**18a**) and (**18b**) (97%), and finally to a 40:60 mixture of phenethyl compounds (**14**) and (**9**) as indicated by its PMR when compared with that of the PMR of pure **9** and **14** obtained above.

Lastly triazole (**4**) was phenacylated to give a crystalline solid, m.p. 115-17° (90%); PMR: 2.36 (3H, *s*), 5.5 (2H, *s*), 7.53 (3H, *m*), 7.9 (2H, *dd*, *J* = 6, 2Hz). Structure (**19**) was assigned to this compound on the

following ground: Hydrogenation over 5% Pd/C in ethanol at 50 psi in the presence of sodium acetate resulted in the formation of a compound identical in all respects with **16a**, m.p. 102° [PMR: 2.23 (3H, *s*), 4.22 (2H, *m*), 5.17 (1H, *m*), 7.33 (5H, *s*), 7.76 (1H, *s*)], obtained by the desulphurisation of **11**. These PMR signals could also be assigned to **16a** in the 40:60 mixture of **16a** and **16b** obtained above.

We have thus prepared several derivatives of 1, 2, 4-triazole of unambiguous structures. It appears from the above work that steric factors play a significant role in directing the entry of the phenacyl group in substituted 1, 2, 4-triazoles. Further work on these lines is in progress.

We thank Drs K R Acharya, S S Tavale and T N Guru Row for the X-ray analysis, the details of which will be published by them elsewhere.

## References

- 1 Meir J & Clemence F, *Fr Demande FR 2,512,022*, (1983) (Roussel-Uclaf); *Chem Abstr*, **99** (1983) 70742.
- 2 Regel E, Buechel K H, Luerssen K & Frohberger P E, *Ger Offen D E 3,108,770* (1982) (Bayer A G); *Chem Abstr*, **98** (1983) 72105j.
- 3 Temple C (Jr), *The chemistry of heterocyclic compounds: Triazoles 1,2,4*, Vol. 37, edited by J.A. Montgomery (John Wiley, New York), 1981, 117, 280, 26, 294.
- 4 Uda M, Hisazumi Y, Sato K, Kubata S, *Chem Pharm Bull*, **24** (1976) 3108.
- 5 Naik S R, Witkowski J T & Robins R K, *J hetero Chem*, **11** (1974) 57.
- 6 Polya J B, *Comprehensive heterocyclic chemistry*, Vol. 5, Part IVa, edited by K.J. Potts (Pergamon Press, Oxford), 1984, 746.
- 7 Reynolds G A & Van Allan J A, *J org Chem*, **24** (1959) 1478.

# Chemistry of Lichen Products: Part V – Synthesis & Antimicrobial Activity of Some New 1,4-Benzoxazinones from Pulvinic Acid Dilactone

K RAGHAVA RAJU & P S RAO\*

Department of Chemistry,  
Kakatiya University, Warangal 506 009

Received 27 September 1984; accepted 31 January 1985

Pulvinic acid dilactone (I) reacts with 2-aminophenols (II) in gl. acetic acid to afford 2-(2,5-dihydro-3-hydroxy-5-oxo-4-phenyl-2-furyl)-2-phenyl-2*H*-1,4-benzoxazin-3(4*H*)-ones (III). The products have been adequately characterized by their analytical and spectral data and their antibacterial and antifungal activities evaluated.

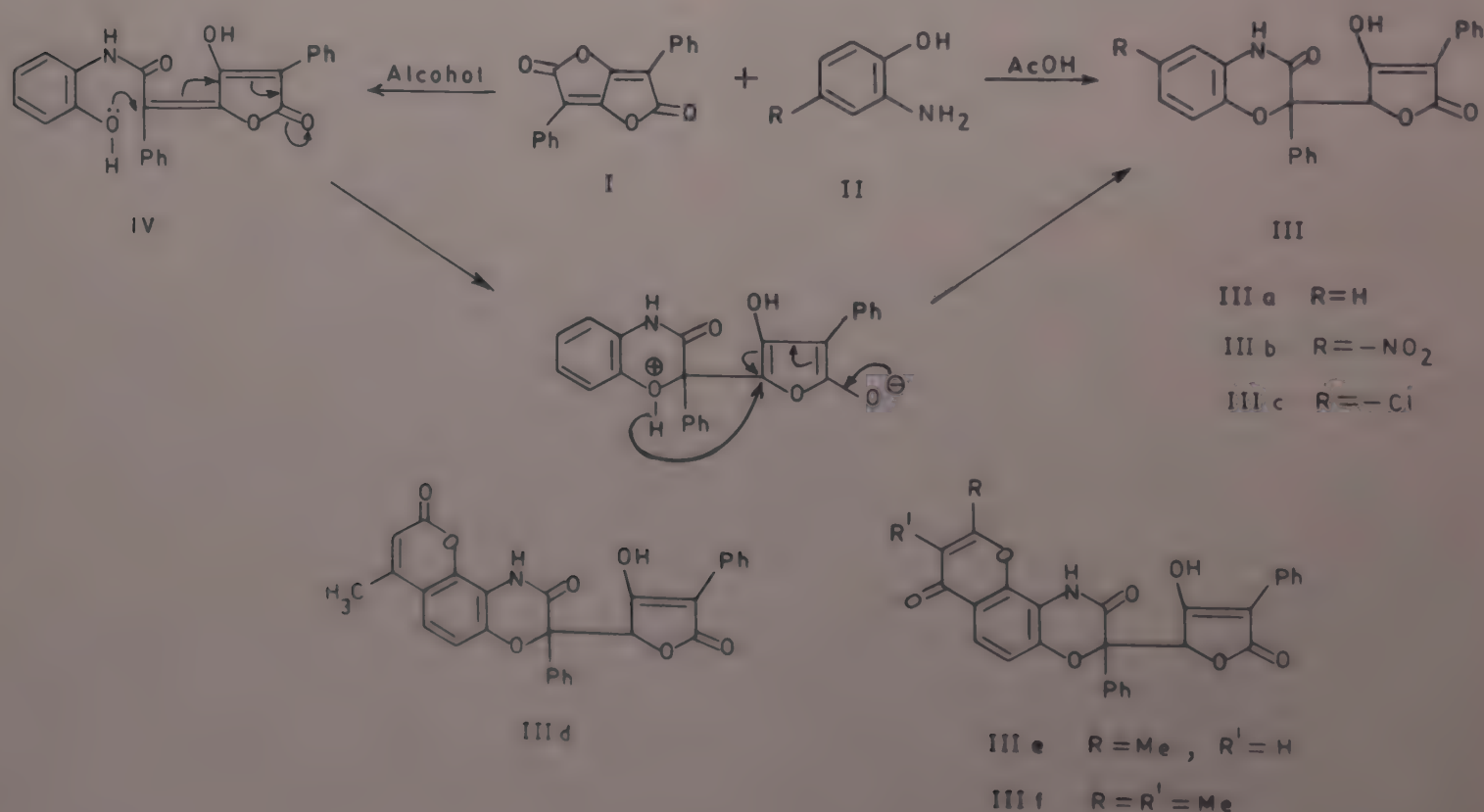
Tetronic acid system is present in many physiologically active naturally occurring substances like vitamin-C, digitoxigenin and the pulvinic group of compounds derived from lichens. In connection with our work<sup>1-4</sup> on modification of lichen substances and screening them for their physiological activity, a few 1,4-benzoxazinones (III) were prepared from pulvinic acid dilactone, a lichen metabolite, by condensing it with various 2-aminophenols (II) as shown in Scheme 1.

Patel *et al.*<sup>5</sup> have reported the synthesis of some 1,4-benzoxazinones by the intramolecular cyclization of

methyl 2-hydroxy-maleanilate in the presence of piperidine acetate in good yields. In the present study a similar type of intramolecular Michael addition of the pulvinic acid anilides (IV), obtained from the reaction of I with II in ethanol, afforded the title compounds (III) in excellent yields by the mechanism shown in Scheme 1.

With a view to following the course of the reaction, 2-aminophenols (IIa-c) were condensed with I in ethanol in the absence of any base or acid catalyst. While the reaction with simple 2-aminophenol (IIa, R = H) yielded the pulvinic acid anilide (IV, R = H), 4-nitro- and 4-chloro-2-aminophenols (IIb and IIc) gave products (IIIb and IIIc) which are similar to those obtained from the reaction in acetic acid medium. It therefore appears that the higher acidity of IIb and IIc causes prototropic rearrangement to form 1,4-benzoxazinones.

The structures of all the compounds were established by their IR, PMR and high resolution mass spectral data. A comparative study of the IR and PMR data of IIIa and IV gave evidence for the presence of 1,4-benzoxazine system in III (Table 1). High resolution mass spectrum of IIIa displayed peaks at *m/z* 384 (A, 1.5%) and 135 (B, 4.0%) (Chart 1) which were absent in the spectrum of pulvinic acid anilide IV (R = H). In addition to these, prominent peaks appeared



Scheme 1

Table I - Characterization Data of 1,4-Benzoxazinones (III) and Pulvinic Acid Anilide (IVa, R = H)

Compd	m.p.* °C	Mol. formula	Found (%) (Calc.)			PMR (DMSO-d <sub>6</sub> )** (δ, ppm)
			C	H	N	
IIIa†	262	C <sub>24</sub> H <sub>17</sub> O <sub>5</sub> N	68.9 (72.1)	3.9 4.2	3.4 (3.5)	6.7-7.6 and 7.9-8.1 (m, 15H, Ar-H and lactone C <sub>5</sub> -H), 8.95 (s, 1H, amide NH), 10.85 (s, 1H, OH)
IIIb	272	C <sub>24</sub> H <sub>16</sub> O <sub>5</sub> NCl	65.5 (66.5)	3.4 3.6	3.2 (3.2)	6.8-7.6 and 8.0-8.5 (m, 14H, Ar-H and lactone C <sub>5</sub> -H), 9.4 (s, 1H, amide NH)
IIIc	253	C <sub>24</sub> H <sub>16</sub> O <sub>7</sub> N <sub>2</sub>	64.2 (64.8)	3.5 3.6	6.2 (6.3)	6.7-7.6 and 8.0-8.5 (m, 14H, Ar-H and lactone C <sub>5</sub> -H), 9.4 (s, 1H, amide NH)
IIId	258	C <sub>28</sub> H <sub>19</sub> O <sub>7</sub> N	67.5 (69.8)	3.8 3.9	2.7 (2.9)	2.4 (s, 3H, CH <sub>3</sub> ), 6.0 (s, 1H, coumarin C <sub>3</sub> -H), 6.8-8.2 (m, 13H, Ar-H and lactone C <sub>5</sub> -H), 9.2 (s, 1H, amide NH)
IIIe	242	C <sub>28</sub> H <sub>19</sub> O <sub>7</sub> N	68.5 (69.8)	3.7 3.9	2.7 (2.9)	2.4 (s, 3H, CH <sub>3</sub> ), 6.0 (s, 1H, chromone C <sub>3</sub> -H), 6.9-8.2 (m, 13H, Ar-H and lactone C <sub>5</sub> -H), 9.2 (s, 1H, amide NH)
IIIf	277	C <sub>29</sub> H <sub>21</sub> O <sub>7</sub> N	69.5 (70.3)	4.0 4.2	2.7 (2.8)	2.4 (s, 3H, CH <sub>3</sub> ), 2.5 (s, 3H, CH <sub>3</sub> ), 6.9-8.2 (m, 13H, Ar-H and lactone C <sub>5</sub> -H), 9.9 (s, 1H, amide NH)
IV‡	238	C <sub>24</sub> H <sub>17</sub> O <sub>5</sub> N	69.5 (70.1)	4.1 4.2	3.3 (3.5)	6.86-8.07 (m, 14H, Ar-H), 8.9 (bs, 1H, amide NH), 9.9 (bs, 1H, phenolic OH), 10.3 (s, 1H, enolic OH)

\* IIIa, IIIb, IIIc, IIIe and IV were recrystallized from methanol and IIId and IIIf from gl. acetic acid.

† IR: 3250 (NH, OH), 1745 (lactone C=O), 1660 (amide C=O), 1605 (C=C), 1230 and 1100 cm<sup>-1</sup> (Ar-O-C-).

‡ IR: 3320 (phenolic OH), 3240 (NH, OH), 1745 (lactone C=O), 1660 (amide C=O), 1615 cm<sup>-1</sup> (C=C).

\*\* The enolic proton in IIIb-IIIf resonated at further downfield.

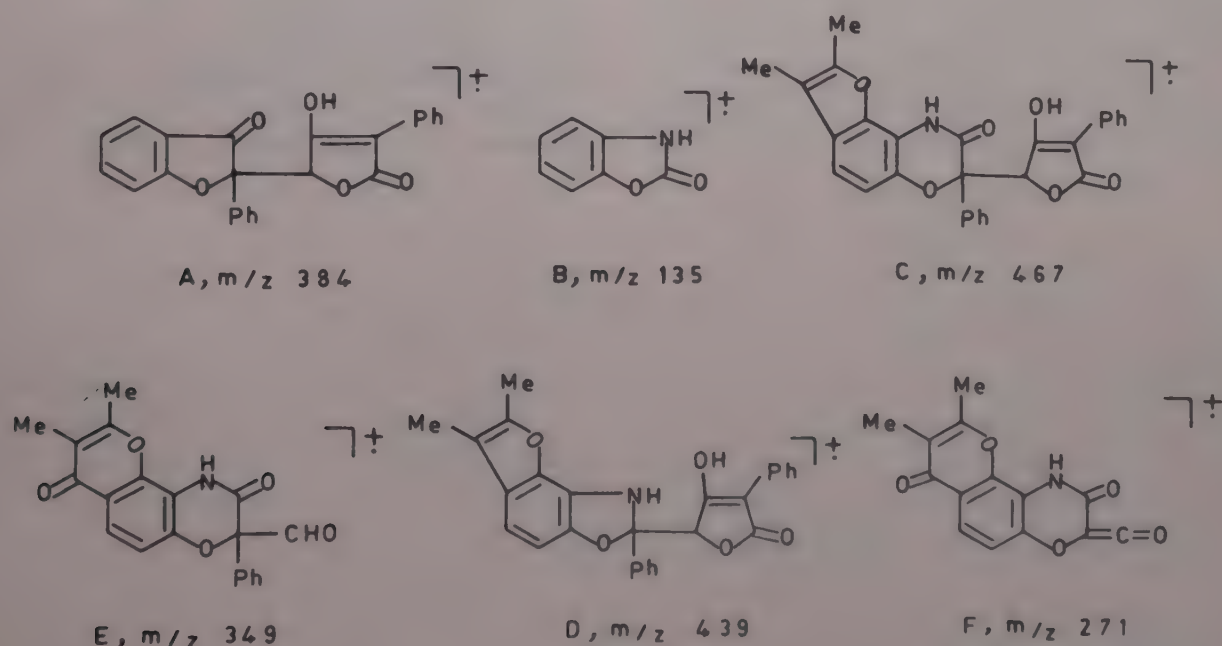


CHART I

at  $m/z$  290 (77.4%), 262 (3.7%), 234 (14.7%), 206 (2.3%), 178 (10.2%), 145 (100%), 117 (53.5%), 89 (94%) and 63 (30.1%) characteristic of pulvinic acid lactone<sup>6</sup> and at  $m/z$  109 due to 2-aminophenol. On the other hand, IV (R = H) gave fragmentation ions at  $m/z$  382 ( $M^+ - OH$ ; 2.1%), 381 ( $M^+ - H_2O$ , 5%), 353 ( $M^+ - CO - H_2O$ , 2.8%) and 336 ( $M^+ - CO - H_2O - OH$ , 1.4%). The other notable feature in the spectrum was the base peak at  $m/z$  109 which indicated the facile formation of 2-aminophenol from the anilide IV (R = H) by the reversal of the reaction. The compound IIIf obtained

by the condensation of I with 8-amino-7-hydroxy-2,3-dimethyl-chromone gave peaks at  $m/z$  495 ( $M^+$ ; 6.3%), 467 (C;  $M^+ - CO$ ; 16.6%), 439 (D;  $M^+ - 2CO$ ; 26.7%), 349 (E;  $M^+ - 145 - H_2$ ; 1.1%) and 271 (F;  $M^+ - 145 - Ph - H_2$ ; 1.6%) (Chart I).

#### Biological activity

The antibacterial activity of the compounds IIIa-f was determined against three gram positive bacteria, viz. *Bacillus polymixa*, *Bacillus pumilus* and *Streptococcus albus* and three gram negative ones, viz. *Proteus*

*vulgaris*, *Pseudomonas ovalis* and *Acetobacter aerogens* by cup-plate method<sup>7</sup>. All the compounds were found to be moderately active against both the types of organisms and relatively more active against gram positive ones. Of all the compounds tested, IIIc and III d exhibited promising activity.

The compounds IIIa-f were also screened for their antifungal activity against *Dreschlera rostrata* and *Alternaria alternata* by spore germination method in acetone<sup>8</sup>. The compound IIIc was relatively more toxic, and *A. alternata* was more susceptible than *D. rostrata* in all the cases. In general, 50% inhibition was achieved at 360-400 µg/ml concentration.

Melting points were determined in open capillaries and uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer 283 instrument, PMR spectra in DMSO-*d*<sub>6</sub> on a Varian EM-390 90 MHz spectrometer using TMS as internal standard and mass spectra on Associated Electrical Industries (AEI MS-9) double-focussing high resolution mass spectrometer and Varian MAT CH-7 instrument at 70 eV.

2-(2,5-Dihydro-3-hydroxy-5-oxo-4-phenyl-2-furyl)-2-phenyl-2H-1,4-benzoxazin-3(4H)-ones (III):

#### General procedure

A mixture of I (0.01 mol) and the corresponding 2-aminophenol (II, 0.01 mol) in gl. acetic acid (50 ml) was either refluxed for 3-4 hr or stirred for 2 hr and left

overnight at room temperature. The crystals which separated out were recrystallised from a suitable solvent to get III (Table I).

#### Pulvinic acid anilide (IV, R = H)

An equimolar mixture of IIa (R = H) (0.01 mol) and I (0.01 mol) in abs. ethanol (50 ml) was warmed on a water-bath till the reactants dissolved. The reaction mixture was left at room temperature for 4 hr and the separated compound crystallised from methanol.

The authors wish to thank Prof. E V Sundaram, Head, Department of Chemistry for providing facilities, Prof. G W Kirby, Glasgow University, Scotland and Prof. G S R Subba Rao, IISc, Bangalore for spectra and to Dr Kurt L Loening, Chemical Abstract Service for naming the compounds.

#### References

- 1 Raghava Raju K & Rao P S, *Indian J Chem*, **24B** (1985) 785; **25B** (1986) 97.
- 2 Raghava Raju K & Rao P S, *Curr Sci*, **53** (1984) 1082.
- 3 Raghava Raju K & Rao P S, *Curr Sci*, **54** (1985) 231.
- 4 Raghava Raju K, Appa Rao A V N & Rao P S, *Fitoterapia*, 1984 (in press).
- 5 Patel M V, Balasubramanian P & Balasubramanian V, *Indian J Chem*, **18B** (1979) 367.
- 6 Letcher R M & Eggers S H, *Tetrahedron lett*, **36** (1967) 3541.
- 7 Arret B, Johnson D P & Kirishabaum A, *J pharm Sci*, **60** (1971) 1689.
- 8 Anonymous, *Phytopathology*, **37** (1947) 3540.

## Chemistry of Lichen Products: Part VI— Synthesis of Some New Benzimidazole Derivatives from Pulvinic Acid Lactone & Their Fungicidal Activity

K RAGHAVA RAJU & P S RAO\*

Department of Chemistry, Kakatiya University, Warangal 506 009

Received 27 September 1984; accepted 31 January 1985

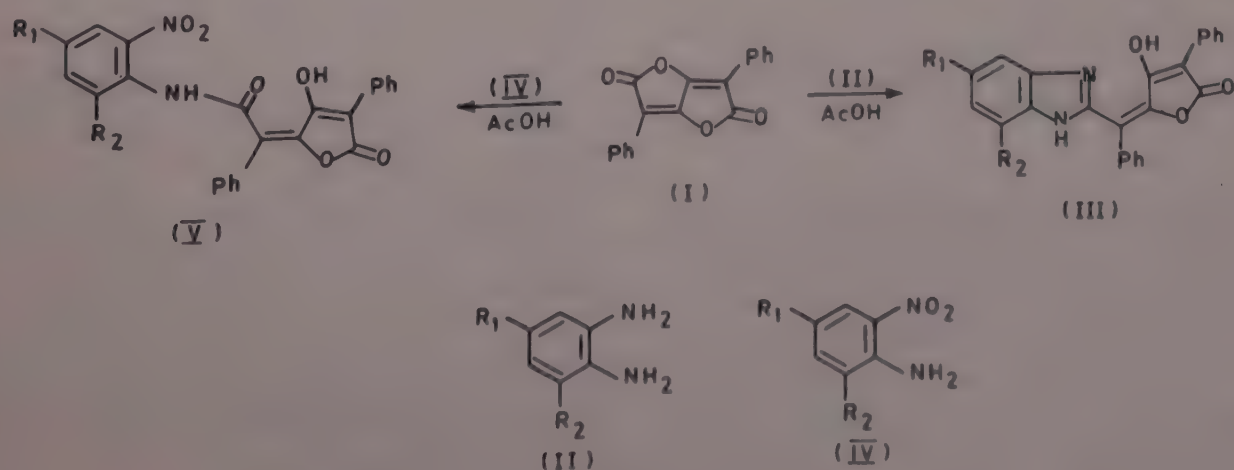
Pulvinic acid lactone (I) reacts with different *o*-phenylenediamines (II) under refluxing in either gl. acetic acid or xylene containing a catalytic amount of piperidine to afford 5-[ $\alpha$ -(2-benzimidazolyl)benzylidene]-4-hydroxy-3-phenyl-2(5*H*)-furanones (III). These benzimidazole derivatives (III) are found to be more fungitoxic than the corresponding pulvinic acid anilides (V) derived from the respective nitroanilines (IV). All the new derivatives have been characterized by their elemental analyses, IR, PMR and mass spectral data.

Compounds related to pulvinic acid are well known<sup>1</sup> for their antiinflammatory activity. In an effort to synthesize potential physiologically active compounds, a few new benzimidazole derivatives (III) have now been prepared from pulvinic acid lactone (I), a lichen metabolite, by condensation with different *o*-phenylenediamines (II, Scheme 1). The required *o*-phenylenediamines were prepared by the reduction of the corresponding nitroanilines (IV). The new pulvinic acid anilides (V) bearing a nitro function were also prepared by the condensation of IV with I in order to compare their biological activity with that of III. The lactone I was prepared according to the procedure of Volhard<sup>2</sup> and compared with an authentic sample obtained from the DMSO-Ac<sub>2</sub>O treatment of polyporic acid<sup>3</sup>.

Condensation of simple *o*-phenylenediamine with various compounds of pulvinic series was carried out by different workers<sup>4-8</sup> using dimethylaniline as solvent and the structures of the product were confirmed on the basis of elemental analyses and IR data only. However, in the present investigation, gl. acetic acid was found to be a very good medium giving the product in more than 70% yield in each case. The reaction was also carried out in anhyd. xylene in the presence of a catalytic amount of pyridine. The pulvinic acid nitroanilides (V, Table 1) gave a green ferric reaction while the corresponding benzimidazoles (III, Table 1) did not show any colouration.

The structures of all the products were established on the basis of their elemental analyses and IR, PMR and high resolution mass spectral data. The compounds V showed IR<sup>†</sup> absorptions at 3260-3300 m (OH, NH), 1760 m (lactone C=O), 1655 m (amide C=O), 1610 s (aliphatic C=C) and 1520 s and 1370 s (—NO<sub>2</sub>). On the other hand benzimidazole derivatives (III) displayed peaks at 3220 br(OH, NH), 1740 s (lactone C=O), 1610 s (—C=N—) and 1605 s (—C=C—) in addition to the skeletal vibrations. The appearance of amide carbonyl band at 1655 and —C=N— vibrations at 1610 supported the structures proposed for V and III respectively.

The compound IIIe was taken as a representative member for PMR<sup>†</sup> and high resolution mass spectral studies. A neat singlet at 2.33 was assignable to the methyl protons of the benzimidazole nucleus. The hydrogen of benzimidazole nitrogen appeared as a broad signal at 6.1. The aromatic protons appeared as two complex clusters, one centered at 7.4 and the other at 8.2 integrating for eleven and two protons



Scheme 1

<sup>†</sup>IR  $\nu_{\max}$  in cm<sup>-1</sup> and PMR chemical shifts in  $\delta$ , ppm throughout the article.

Table 1—Characterization Data of Compounds III and V

Compd	R <sub>1</sub>	R <sub>2</sub>	m.p. °C	Crystallized from	Yield (%)	Mol. formula	Found (%) (Calc.)		
							C	H	N
IIIa	H	H	312	Me <sub>2</sub> CO	75	C <sub>24</sub> H <sub>16</sub> O <sub>3</sub> N <sub>2</sub>	75.3 (75.7)	3.9 (4.2)	6.1 (7.3)
IIIb	Br	Br	>315	AcOH	80	C <sub>24</sub> H <sub>14</sub> O <sub>3</sub> N <sub>2</sub> Br <sub>2</sub>	53.2 (53.5)	2.5 (2.6)	5.1 (5.2)
IIIc	Cl	Cl	303	AcOH	80	C <sub>24</sub> H <sub>14</sub> O <sub>3</sub> N <sub>2</sub> Cl <sub>2</sub>	63.8 (64.1)	2.9 (3.1)	5.7 (6.2)
IIId	H	CH <sub>3</sub>	>315	AcOH	85	C <sub>25</sub> H <sub>18</sub> O <sub>3</sub> N <sub>2</sub>	75.8 (76.1)	4.3 (4.5)	6.8 (7.1)
IIIe	CH <sub>3</sub>	H	262	Me <sub>2</sub> CO	75	C <sub>25</sub> H <sub>18</sub> O <sub>3</sub> N <sub>2</sub>	75.8 (76.1)	3.9 (4.5)	6.9 (7.1)
IIIf	OCH <sub>3</sub>	H	246	Me <sub>2</sub> CO	65	C <sub>25</sub> H <sub>18</sub> O <sub>4</sub> N <sub>2</sub>	72.9 (73.1)	3.9 (4.3)	6.5 (6.8)
IIIg	Br	H	265	AcOH	62	C <sub>24</sub> H <sub>15</sub> O <sub>3</sub> N <sub>2</sub> Br	62.2 (62.7)	2.9 (3.2)	5.9 (6.1)
Va	Br	Br	125	EtOH	65	C <sub>24</sub> H <sub>14</sub> O <sub>6</sub> N <sub>2</sub> Br <sub>2</sub>	48.8 (49.1)	2.2 (2.3)	4.5 (4.7)
Vb	Cl	Cl	105	EtOH	65	C <sub>24</sub> H <sub>14</sub> O <sub>6</sub> N <sub>2</sub> Cl <sub>2</sub>	57.8 (57.9)	2.8 (2.8)	5.2 (5.6)
Vc	CH <sub>3</sub>	H	244	AcOH	75	C <sub>25</sub> H <sub>18</sub> O <sub>6</sub> N <sub>2</sub>	67.5 (67.8)	4.0 (4.0)	6.1 (6.3)
Vd	OCH <sub>3</sub>	H	215	AcOH	70	C <sub>25</sub> H <sub>18</sub> O <sub>7</sub> N <sub>2</sub>	65.2 (65.4)	3.7 (3.9)	5.9 (6.1)
Ve	H	CH <sub>3</sub>	235	AcOH	68	C <sub>25</sub> H <sub>18</sub> O <sub>6</sub> N <sub>2</sub>	67.5 (67.8)	3.8 (4.0)	6.1 (6.3)

respectively. The enolic proton resonated at 13.6. The hydrogens attached to nitrogen and oxygen were exchangeable with D<sub>2</sub>O.

The high resolution mass spectra of the compounds IIId and IIIe displayed a prominent M<sup>+</sup> peak at *m/z* 394 corresponding to the molecular formula C<sub>25</sub>H<sub>18</sub>O<sub>3</sub>N<sub>2</sub>. The base peak was observed at *m/z* 249 in either case. This peak appears to have resulted from the loss of 145 mass units due to a phenyl ketone moiety which often appears as a base peak in the spectra of most of the pulvinic acid derivatives<sup>9</sup> followed by a hydrogen rearrangement. The fragmentation pattern (Chart 1) of IIIe was well supported by the elemental composition offered by accurate mass measurements.

#### Biological activity

The fungicidal activity of compounds III and V was determined against *Drechslera rostrata* and *Alternaria alternata* by spore germination method in acetone<sup>10</sup>. In general the benzimidazole derivatives (III) were found to be more fungitoxic than the corresponding pulvinic acid anilides (V). Out of the benzimidazole derivatives screened, IIIb and IIIc inhibited the growth completely at 200 µg/ml concentration, while the compounds IIIa, IIId and IIIg exhibited moderate activity, and IIIe and IIIf were almost inactive. Among the nitroanilides, the halogen substituted compounds

(Va and Vb) were more toxic compared to other members.

Melting points were determined in open capillaries and uncorrected. Homogeneity of the compounds was checked by TLC on plates coated (0.25 mm) with silica gel G using toluene-acetic acid (9:1 v/v) as irrigant. IR spectra were recorded in nujol on a Perkin-Elmer 283 instrument, PMR spectra in DMSO-*d*<sub>6</sub> on a Varian EM-390 90 MHz spectrometer using TMS as internal standard and mass spectra on a Associated Electrical Industries (AEI MS-9) double focussing high resolution mass spectrometer at 70 eV.

#### 5-[α-(2-Benzimidazolyl)benzylidene]-4-hydroxy-3-phenyl-2(5H)-furanones (III, Table 1)

##### (a) In acetic acid medium

To a solution of I (0.01 mol) in gl. acetic acid (50 ml), substituted *o*-phenylenediamine (II) or its hydrochloride (0.015 mol) was added and the reaction mixture refluxed for 5 hr, cooled when the product separated out in a pure state. It was filtered and recrystallised from a suitable solvent.

##### (b) In xylene/piperidine medium

Compound I and simple *o*-phenylenediamine in equal proportions (0.01 mol each) were taken in xylene (30 ml) containing a few drops of piperidine and refluxed for 4 hr. Xylene was removed under reduced

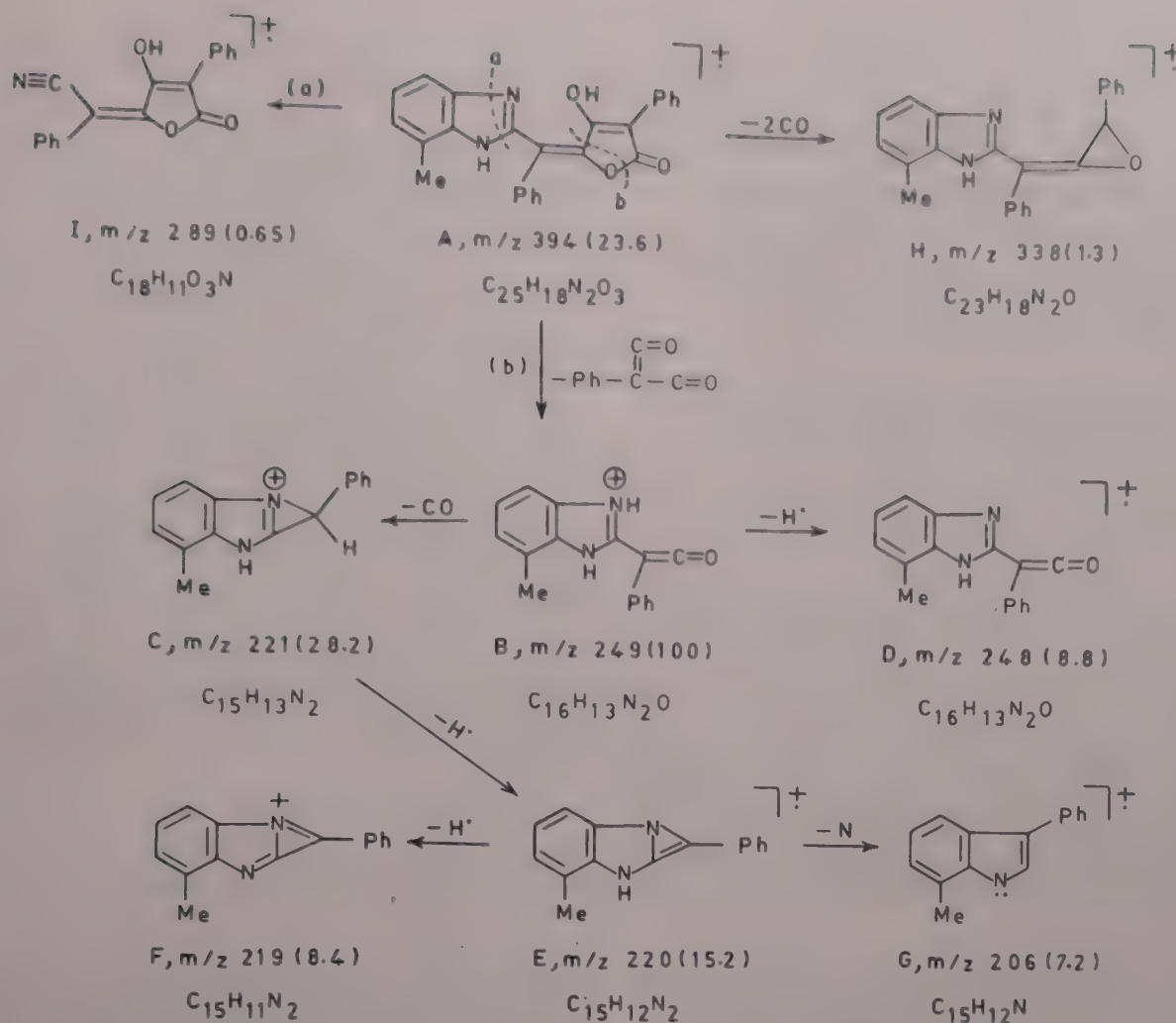


CHART I

pressure to get IIIa as an orange coloured compound which crystallised from acetone, m.p.  $312^\circ$ .

#### Pulvinic acid anilides (V, Table 1)

Equimolar quantities of I (0.01 mol) and substituted nitroaniline (IV, 0.01 mol) were taken in gl. acetic acid (75 ml) and the mixture was gently refluxed for 2-3 hr. The resulting bright yellow coloured solution was poured into crushed ice, the solid thus obtained filtered off, washed successively with dil. HCl and water and recrystallized from an appropriate solvent.

The authors are grateful to Prof E V Sundaram, Head, Department of Chemistry, Kakatiya University, Warangal and Dr D J Robins, Glasgow University, Scotland for providing facilities and spectral data respectively. One of the authors (P S R) is

grateful to the UGC, New Delhi for financial assistance.

#### References

- 1 Sutton B M, *Chem Abstr*, **80** (1974) 82624v; **80** (1974) 133047u; **81** (1974) 91365j.
- 2 Volhard J, *Liebig's Ann*, **282** (1894) 1.
- 3 Frank R L, Clark G R & Coker J N, *J Am chem Soc*, **72** (1950) 1824.
- 4 Schonberg A & Sina A, *J chem Soc*, (1946) 601.
- 5 Agarwal S C & Seshadri T R, *Tetrahedron*, **20** (1964) 24.
- 6 Grover P K & Seshadri T R, *J chem Soc*, (1960) 2134; *Tetrahedron*, **6** (1959) 312.
- 7 Karrer P, Gehrekens K A & Heuss D W, *Helv chim Acta*, **9** (1926) 446.
- 8 Mittal O P & Seshadri T R, *J chem Soc*, (1955) 3053; (1956) 1734.
- 9 Letcher R M & Eggers S H, *Tetrahedron Lett*, **36** (1967) 3541.
- 10 Anonymous, *Phytopathology*, **37** (1947) 3540.

Chemical Examination of *Premna*  
Species: Part XI<sup>a</sup>—Structure of  
Premnoside-A from *Premna latifolia*  
Roxb. (var. *cuneata*)<sup>b</sup>

CH BHEEMASANKARA RAO\*, P GOPALA KRISHNA,  
P ARUNA DEVI & G V SUBBA RAJU<sup>c</sup>

School of Chemistry, Andhra University, Visakhapatnam 530 003  
and

V MOHAN CHARI

Department of Internal Medicine, University of Texas Medical  
School, Houston, TX 77025, USA

Received 27 May 1985; accepted 24 June 1985

Premnoside-A, a flavone bioside from the leaves of *Premna latifolia* Roxb. (var. *cuneata*) has been characterised as 7-O-[ $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-O- $\alpha$ -L-arabinopyranosyl]-5-hydroxy-4'-methoxyflavone based on chemical and spectral evidence. Several other known compounds have also been isolated and characterised.

In an earlier communication<sup>2</sup> we described the isolation and partial structure of a flavone bioside, premnoside-A, from the leaves of *Premna latifolia* Roxb. We present in this note, evidence for the interglycosidic linkage of the bioside. In addition, several known compounds from *Premna latifolia* (var. *cuneata*) are also reported.

Premnoside-A was reported to contain 4'-O-methylapigenin (acacetin) as aglycone and rhamnose and arabinose as sugars. Partial hydrolysis of premnoside-A with 1% aq. sulphuric acid or with modified Killiani mixture<sup>3</sup> afforded a monoside, m.p. 208-11°, C<sub>21</sub>H<sub>20</sub>O<sub>9</sub>, characterised as acacetin-7-O-arabinoside by hydrolytic cleavage and spectral data. Premnoside-A, thus be described as acacetin-7-O-rhamnosylarabinoside. The ring size and configuration of sugar units and the site of interglycosidic linkage were ascertained from <sup>1</sup>H NMR and <sup>13</sup>C NMR data. Premnoside-A, on complete acetylation yielded the hexaacetyl derivative, C<sub>39</sub>H<sub>42</sub>O<sub>19</sub>, m.p. 140-43°.

The coupling constant of anomeric proton (<sup>3</sup>J<sub>H-1,H-2</sub> = 2 Hz) of rhamnose in premnoside-A and the chemical shift of C-1 of rhamnose (100.5 ppm) favour  $\alpha$ -pyranose form<sup>4,5</sup>. The chemical shift of C-4 of

arabinose (67.7 ppm in premnoside-A and 67.0 in monoside) points to pyranose form<sup>4,6</sup>. The coupling constants of the anomeric proton (<sup>3</sup>J<sub>H-1,H-2</sub>) of arabinose moiety in premnoside-A (8.0 Hz) and monoside (6.2 Hz) favour  $\alpha$ -configuration<sup>5,7</sup>. Premnoside-A consumed 2.8 mol of periodate on oxidation consistent with the presence of three glycol units in pyranose form of sugar moieties.

The downfield shift of about 4.0 ppm of C-2 and the upfield shift of 1.8 ppm of C-1 of arabinose unit in the CMR spectrum of premnoside-A compared to those in the monoside establishes the 1 $\rightarrow$ 2 interglycosidic linkage<sup>4</sup>. The chemical shift of C-7 in the bioside (162.4 ppm) as well as in the monoside (162.7 ppm) supports 7-O-glycosylation<sup>4</sup>.

From the foregoing, premnoside-A may be constituted as 7-O-[ $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-O- $\alpha$ -L-arabinopyranosyl]-5-hydroxy-4'-methoxyflavone.

Mass spectrum of neither premnoside-A nor its permethylether showed the molecular ion; however, the diisopropylidene permethylether exhibited the molecular ion (M<sup>+</sup>) at m/z 670 and important fragment ions exhibiting fragmentation<sup>8</sup> in full support of the above structure.

The residues from the extracts of wood of *P. latifolia* (var. *cuneata*) on chromatography gave 6,8-di-C- $\beta$ -D-glucopyranosylapigenin (vicenin-2)<sup>9</sup>, 1-triacontanol<sup>10</sup> and D-glucose. Other known compounds isolated from the leaves of *P. latifolia* (var. *cuneata*) include premnalatin<sup>11</sup>, sesamin<sup>12</sup>, dipiperonylthane<sup>13</sup>, aurantiamide and its acetate<sup>14</sup> and  $\beta$ -sitosterol-3-O-glucoside. The identity of known compounds was established by comparison with authentic samples.

The authors thank the CSIR and UGC, New Delhi for the award of fellowships to GVSR, PGK and PAD.

## References

- 1 Rao Ch B, Krishna P G & Suseela K, *Indian J Chem*, **24B** (1985) 403.
- 2 Rao Ch B & Raju G V S, *Curr Sci*, **50** (1981) 180.
- 3 Sharma A, Chibber S S & Chawla H M, *Indian J Chem*, **19B** (1980) 237.
- 4 Markham K R & Chari V M, in *The flavonoids, advances in research*, edited by J B Harborne & T J Mabry (Chapman & Hall, London), 1982, 303.
- 5 Hase T, Uchio Y & Kubota T, *Nippon Kagaku Kaishi*, (1977) 529.
- 6 Goren P A J & Mazurek M, *Can J Chem*, **53** (1975) 1212.
- 7 Ishii H, Kitagawa I, Matsushita K, Shiwakawa K, Tori K, Tozjo T, Yoshikawa M & Yoshimura Y, *Tetrahedron Lett*, (1981) 1529.
- 8 Schmid R D, *Tetrahedron*, **28** (1972) 3259.

<sup>a</sup>Part X see ref. 1

<sup>b</sup>Presented at 23rd Annual Meeting of the Phytochemical Society of North America, University of Arizona, Tucson, Arizona, U.S.A., July, 1984

<sup>c</sup>Present address: Chemistry Department, S.V. University, Tirupati 517 502

# NOTES

- 9 Osterdahl B G, *Acta chem Scand*, **B32** (1978) 93; Bouilliant M L, Ferreres De Arce F, Favre-Bonvin, Chopin J & Mathieu A Z G, *Phytochemistry*, **18** (1979) 1043.
- 10 Ries S K & Wert W, *Science*, **195** (1977) 1339; Maruyama K, Terada K & Yamamoto, *J org Chem*, **45** (1980) 737.
- 11 Rao Ch B & Vijayakumar E K S, *Indian J Chem*, **19B** (1980) 240.
- 12 Takahashi K & Nakagawa T, *Chem pharm Bull*, **14** (1966) 641.
- 13 Bruchhausen F V & Linger K, *Arch Pharm*, **290** (1957) 1.
- 14 Banerji A & Das R, *Indian J Chem*, **13** (1975) 1234; *Phytochemistry*, **20** (1981) 2217.

## Addition of 4-Hydroxycoumarin to $\alpha,\beta$ -Unsaturated Carbonyl Derivatives & Mannich Base Methiodides Derived from Cyclic Ketones†

VIJAY KHANNA, SUNIL R PARASKAR & P H LADWA\*

Postgraduate School for Biological Studies,  
Ahmednagar College, Ahmednagar 414001

and

M B BHIDE

Indian Institute of Toxicology, Bombay 400001

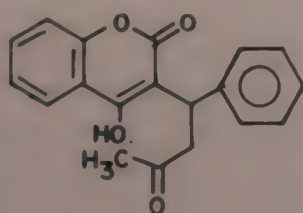
Received 26 April 1984; accepted 7 January 1985

Five new 4-hydroxycoumarins incorporating a cyclic ketone have been synthesized, their structures established by PMR, IR and UV spectral data, and screened for their anticoagulant activity.

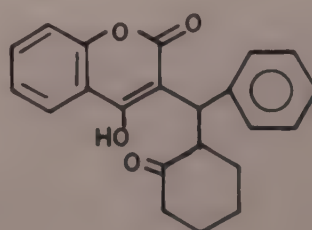
Michael addition of 4-hydroxycoumarin to benzalacetone yields the well known anticoagulant rodenticide warfarin<sup>1</sup>, 3-(2-acetyl-1-phenethyl)-4-hydroxycou-

marin (I). The new rodenticides belonging to warfarin group of compounds have become necessary since resistance has occurred in some cases<sup>2,3</sup>. It is, thus, interesting to synthesize warfarin like compounds (II to VII) since these represent much more radical variation in the side chain. It is significant to note that the compounds IV and VII are optically active and it is well established that S-(–) warfarin<sup>4,5</sup> has better anticoagulant activity than the other isomers of warfarin. The optically active anticoagulants/rodenticides bearing a terpene moiety incorporated with suitable functional groups which could possibly lead to the hemiketal formation *in vivo*<sup>6</sup>, represent an important class of compounds and have not been explored in drug design. We report here in the synthesis of such five analogs.

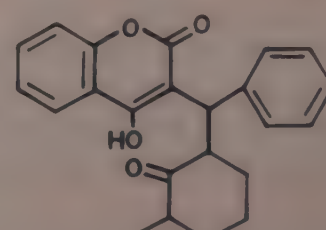
2-Benzylidenecyclohexanone (IX), 2-benzylidene-6-methyl-cyclohexanone (X) and 2-benzylidene-6-isopropyl-3-methylcyclohexanone (XI) ( $[\alpha]_D^{28} - 195^\circ$ )



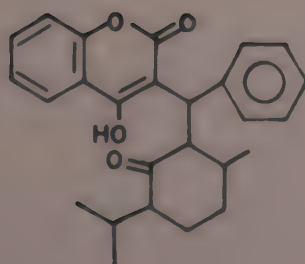
(I)



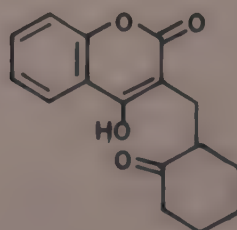
(II)



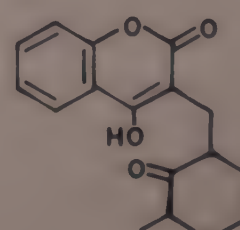
(III)



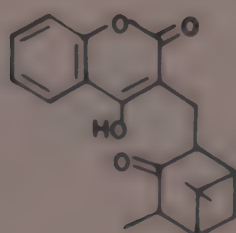
(IV)



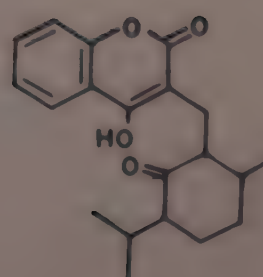
(V)



(VI)



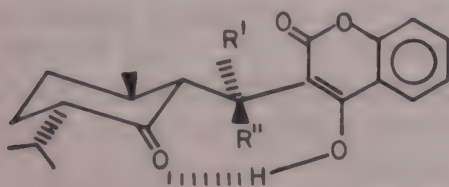
(VII)



(VIII)

†Part II of the series 'Chemistry of Anticoagulants'.

underwent Michael addition with 4-hydroxycoumarin in dioxane containing a catalytic amount of piperidine to yield compounds II, III and IV respectively. The hydrogen bonding between hydroxyl group and carbonyl group would force the compound IV to take up two diastereoisomeric forms **A** and **B**. The dreiding model of diastereoisomer **A** clearly indicates that 7'-methyl protons are deep in the shielding zone of ring currents of the phenyl group, and it is for this reason it appears upfield at 0.5  $\delta$  ppm. Hence, compound IV has the stereochemistry as depicted in **A**. Similar attempts to effect Michael addition of 4-hydroxycoumarin with



benzylidenecaranone and benzylidenepinanone gave, instead of the desired products, 4-piperidinocoumarins.

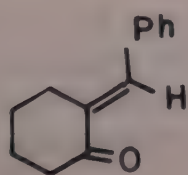
In our earlier communication we have reported the synthesis of 4-hydroxy-3-( $\alpha$ -2-*p*-menthylmethyl)coumarin (VIII) by addition of 4-hydroxycoumarin to the Mannich base methiodide of *R*-( $-$ )-menthone (XI) in the presence of triethylamine and acetonitrile. This study has been extended to the synthesis of 4-hydroxy-3-(2-oxo-cyclohexylmethyl)coumarin (V), 4-hydroxy-3-(3-methyl-2-oxo-cyclohexylmethyl)coumarin (VI) and 4-hydroxy-3-(3-oxo-pinanylmethyl)coumarin (VII).

Thus the Mannich base methiodides prepared from cyclohexanone (XII), 2-methylcyclohexanone (XIII) and pinan-3-one (XIV) reacted with 4-hydroxycoumarin in the presence of triethylamine and acetonitrile to yield compounds V, VI and VII respectively. All the products were purified by chromatography over silica gel G followed by recrystallisation from suitable solvents. Similar attempts to effect addition of 4-hydroxycoumarin to the Mannich base methiodides of 4-isocaranone and camphor did not furnish the desired product.

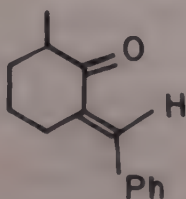
#### Anticoagulant activity

Mice of either sex weighing between 20 and 25 g were used. The compounds were suspended in water using carboxymethylcellulose (CMC) as medium and

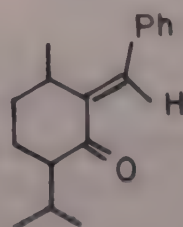
STEREISOIMER	R'	R''
<b>A</b>	PHENYL	H
<b>B</b>	H	PHENYL



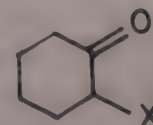
(IX)



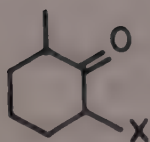
(X)



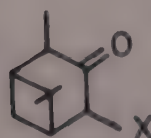
(XI)



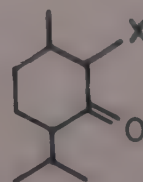
(XII)



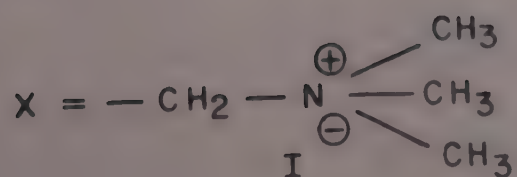
(XIII)



(XIV)



(XV)



injected i.p. in a dose of 50 mg/kg per day for 3 days. Warfarin (I) in a dose of 5 mg/kg was used as a standard. The control group was given only vehicle. On the 4th day the clotting time was recorded by the capillary method as described below. The blood was collected in a fine glass capillary by piercing it through the orbital sinus of the animal. The capillary was broken by hand, gently, every 10-15 second till a thread like clot appeared. The time between piercing of the orbital sinus and appearance of clot was noted which was taken as the clotting time.

Table 1 shows the average clotting time in mice for the compounds studied. Average clotting time of control animals was about 60 seconds and that of warfarin treated animals was about 137.5 seconds. Among the compounds screened only compound V showed significant prolongation of clotting time. All other compounds appeared to be inactive.

*Benzylidenecyclohexanones (IX, X, XI): General procedure*

Benzaldehyde (0.1 mol) and appropriate cyclic ketone (0.1 mol) were dissolved in abs ethanol containing catalytic amount (0.3g) of KOH. The reaction mixture was left in the dark for 4 days, ethanol removed using rotary evaporator *in vacuo* and the residue dissolved in ether. Usual work-up of ether extract followed by distillation *in vacuo* afforded the corresponding benzylidene derivative in 80-90% yield.

*Michael addition of coumarin to benzylidene derivatives: Formation of II, III and IV*

The appropriate benzylidenecyclohexanone (0.1 mol) and 4-hydroxycoumarin (0.1 mol) were dissolved in dioxane (100 ml) containing piperidine in catalytic amount. The reaction mixture was refluxed gently till completion of reaction as shown by TLC. Dioxane was removed *in vacuo* and the residue extracted with chloroform. Usual work-up followed by chromatography over silica gel G using pet. ether-ethyl acetate as eluent yielded the desired products in pure state. Their characterisation data are as follows:

4-Hydroxy-3-[ $\alpha$ -(2-oxo-cyclohexyl)benzyl] coumarin (II): m.p. 216-17; analysed for  $C_{22}H_{20}O_4$  ( $M^+$  348); IR $\dagger$  (nujol): 3320 (OH), 1710 (C=O), 1690 (coumarin C=O), 1630 (enolic double bond), 1605 and 1570 (aromatic  $>C=C<$ ) and 770-735 (aromatic C-H); UV $\dagger$  (methanol): 304 ( $\epsilon$ , 12460), 281 (13840) and 271 (12456) (absorption peaks of 4-hydroxycoumarins); PMR $\dagger$  ( $CDCl_3$ ) 1.4-2.2 (bm, 10H,  $4 \times CH_2$  and  $2 \times CH$ ) and 7.3 (bs, 9H, Ar-H).

4-Hydroxy-3-[ $\alpha$ -(methyl-2-oxo-cyclohexyl) benzyl] coumarin (III): m.p. 169-70; analysed for  $C_{23}H_{22}O_4$

Table 1—Anticoagulant Activity of Compounds II-VIII

Compound	*Average clotting time (s)	Compound	*Average clotting time (s)
Control	60.0	V	115.0
I (Standard)	137.5	VI	61.6
II	51.6	VII	83.75
III	74.1	VIII	73.7
IV	55.8		

\*A total of 6 animals were used per group.

( $M^+$  362); IR (nujol): 3356 (OH), 1710 ( $>C=O$ ), 1689 (coumarin  $>C=O$ ), 1639 (enolic double bond), 1610 and 1543 (aromatic  $>C=C<$ ) and 770-735 (aromatic C-H); UV (methanol): 305 ( $\epsilon$  12000), 281 (13780) and 271 (12400); PMR ( $CDCl_3$ ): 1.05 ( $d$ ,  $J=7$ Hz, 3H,  $CH_3$ ), 7.3 (bs, 9H, Ar-H).

4-Hydroxy-3-[ $\alpha$ -(3-oxo-2-p-methyl)benzyl] coumarin (IV): m.p. 214° [ $\alpha$ ] $_D^{28} - 80.6^\circ$  ( $CHCl_3$ ), analysed for  $C_{26}H_{28}O_4$  ( $M^+$  404); IR (nujol): 3425 (OH), 1712 ( $>C=O$ ), 1681 (coumarin  $>C=O$ ), 1634 (enolic double bond), 1610 (aromatic  $>C=C<$ ) and 770-735 (aromatic C-H); UV (methanol): 308 ( $\epsilon$  12697), 282 (12300); PMR ( $CDCl_3$ ): 0.5 ( $d$ ,  $J=6$ Hz, 3H,  $CH_3$ ), 0.8 ( $d$ ,  $J=6$ Hz, 3H,  $CH_3$ ), 1.1 ( $d$ ,  $J=6$ Hz, 3H,  $CH_3$ ), 7.23 (bs, 5H,  $C_6H_5$ ), 7.4 ( $s$ , 4H, Ar-H).

*Addition of coumarin to the Mannich base methiodides: Formation of V, VI and VII*

The same procedure as given by us in an earlier communication<sup>7</sup> was used. The characterisation data of V-VII are given below: Compound V gave correct C and H analysis and its m.p. (192°) matches with that in the literature<sup>9</sup>.

4-Hydroxy-3-(1-methyl-2-oxo-cyclohexylmethyl) coumarin (VI): m.p. 165°; analysed for  $C_{17}H_{18}O_4$  ( $M^+$  286); IR (nujol): 3430 (OH), 1715 ( $>C=O$ ), 1680 (coumarin  $>C=O$ ), 1630 (enolic double bond), 1570 and 1490 (aromatic  $>C=C<$ ), 770-735 (aromatic C-H); UV (methanol): 308 ( $\epsilon$  12420), 281 (13800) and 269 (12400); PMR ( $CDCl_3$ ): 1.05 ( $d$ ,  $J=7$ Hz, 3H,  $CH_3$ ), 7.3 (bs, 4H, Ar-H).

(-)-4-Hydroxy-3-(3-oxo-pinanylmethyl) coumarin (VII): m.p. 120-22°; [ $\alpha$ ] $_D^{28} - 15.67^\circ$  ( $CHCl_3$ ); analysed for  $C_{20}H_{22}O_4$  ( $M^+$  326); IR (nujol): 3380 (OH), 1710 ( $>C=O$ ), 1680 (coumarin  $>C=O$ ), 1630 (enolic double bond), 1570 and 1490 (aromatic  $>C=C<$ ), 770-735 (aromatic C-H); UV (methanol): 308 ( $\epsilon$  12600), 283 (14060) and 270 (12460); PMR ( $CDCl_3$ ): 1.0 ( $s$ , 3H,  $CH_3$ ), 1.23 ( $d$ ,  $J=7$ Hz, 3H,  $CH_3$ ), 1.42 ( $s$ , 3H,  $CH_3$ ), 7.2 ( $m$ , 4H, Ar-H).

The authors are thankful to the UGC, New Delhi and BPHE society, Ahmednagar College, Ahmednagar for financial assistance. They are also thankful

$\dagger$  IR,  $\nu_{max}$  in  $cm^{-1}$ ; PMR, chemical shifts in  $\delta$ , ppm and UV,  $\lambda_{max}$  in nm throughout the article.

to Dr S N Kulkarni, NCL, Pune and R S Joshi, Indian Institute of Toxicology, Bombay for useful discussion.

# References

- 1 Link K P, *Fed Proc US*, 176182 (1945).
- 2 Renapurkar D M & Kamath Vijaylaxmi R, *Bull Haff Inst*, 10 (1982) 17.
- 3 William B. Jackson & Dele Kauchainen, *Science*, 176 (1972) 1343.
- 4 O'Reilly Robert A, *Clin Pharmacol Ther*, 16 (1974) 348.
- 5 Bell Robert G & Ren Peter, *Biochem Pharmacol*, 30 (1981) 1953.
- 6 Chmielewska I & Cieslak J, *Tetrahedron*, 4 (1958) 135.
- 7 Paraskar S R & Ladwa P H, *Indian J Chem*, 22B (1983) 829.
- 8 Shah R & Bose J L, *J org Chem*, 25 (1960) 677.
- 9 Zelimer Prochazka, *Czech* 85 (1955) 358.

## *p*-(Cyclopentenyl)phenol Derivatives as Potential Biodynamic Agents†

SURAT KUMAR & SHRI NIVAS RASTOGI\*

Division of Medicinal Chemistry, Central Drug Research Institute,  
Lucknow 226 001

Received 6 August 1984; accepted 17 October 1984

Aminomethylation and alkylation of *p*-(cyclopent-1/2-enyl)-phenols (1, 3) affords *o*-aminomethylphenols (4-7) and aryl alkyl ethers (8-13 and 20) respectively. Condensation of 3-chloropropoxy compounds (8 and 12) and the epoxides 20 and 27 with amines yields 3-substituted aminopropanes/propanols (14-17, 19, 21-26 and 28). Among these, compounds 16 and 17 on treatment with HCl-AcOH give the same product (18). Compounds 10-12, 14, 16-19 and 22 exhibit antiarrhythmic activity.

It has been reported<sup>1-3</sup> that 1-(*o*-cyclopentylphenoxy)-3-(*t*-butylamino)propan-2-ol (penbutolol) and 1-(*o*- and *p*-cyclopent-2-en-1-yl)-3-(*t*-butylamino)propan-2-ols possess varying degrees of  $\beta$ -adrenergic blocking and antiarrhythmic activities and 1-(*m*-acetylphenoxy)-3-[(4-hydroxy-4-phenyl piperidyl]propane<sup>4</sup>, the most active amongst *o*-, *m*-, and *p*-alkanoylphenoxy derivatives<sup>4</sup>, provides protection against arrhythmias induced by aconitine in rats and is more effective than quinidine at 5 mg/kg i.v. dose in suppressing electrically induced ventricular fibrillation in anaesthetised cats. To improve upon these activities, we have undertaken further exploration of this series. We report herein the synthesis and screening results of *p*-(cyclopent-1/2-enyl)phenol derivatives.

Aminoethylation of *p*-(cyclopent-1/2-enyl)phenols<sup>5</sup> (1 and 3) with various amines gave the corresponding *p*-cyclopentenyl-*o*-aminomethylphenols (4, 5 and 7), of which 5 with phenyl isocyanate afforded its carbamate (6). Alkylation of 1 and 3 with allyl bromide, bromochloropropane, dibromopropane, ethyl bromoacetate and epichlorohydrin in the presence of K<sub>2</sub>CO<sub>3</sub> yielded the corresponding  $\omega$ -substituted-alkyl cyclopentenylphenyl ethers (8-12) and epoxide the 21. Treatment of 3 with acrylonitrile in the presence of triton-B gave its propionitrile derivative (13). Condensation of 8, 12, 20 and 27<sup>3</sup> with various amines afforded the corresponding 3-substituted-aminopropanes/propan-2-ols (14-17, 19, 21-25 and 28; Scheme 1). Acetylation of 22 (N < = NHMe<sub>3</sub>, R = H) with Ac<sub>2</sub>O-pyridine gave the diacetyl derivative (26). Refluxing of 4-hydroxy-4-phenylpiperidyl compounds

(16 and 17) with HCl-AcOH brought about dehydration in 17 and also the isomerisation of the double bond in 16, to yield only 3-(4-phenyl-3-piperidienyl)cyclopent-1-enylpropane (18) in both the cases (Scheme 1).

Therefore, the corresponding *p*-cyclopent-2-en-1-yl phenyl compound 19 was prepared by the reaction of 8 with 4-phenyl-3,4-dehydropiperidine. The characterization data of compounds 4-28 are given in Table 1.

### Pharmacological activity

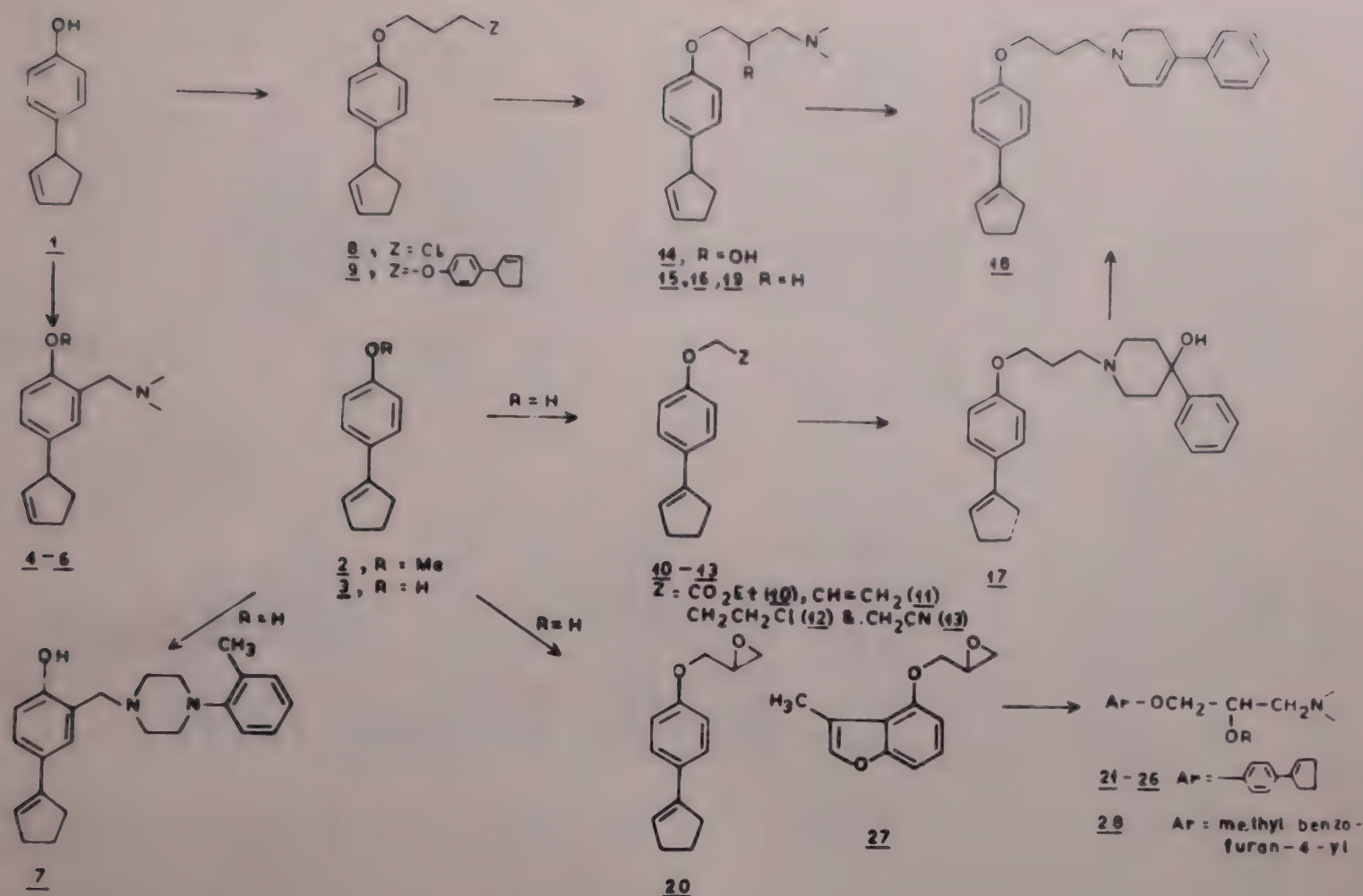
The gross behavioural effects and acute toxicity (ALD<sub>50</sub>) were studied<sup>6</sup> in albino mice by i.p. administration of graded doses of the compounds using five animals per dose. The effect on blood pressure and respiration and interaction with acetylcholine and epinephrine were studied in anaesthetized cats (pentobarbitone, 35 mg/kg). The *in vitro* antiarrhythmic activity was tested by the method of Dawes<sup>7</sup> in isolated guinea pig auricle, and PCA and diuretic activities were determined by standard methods<sup>8</sup>. Antiinflammatory and  $\beta$ -adrenoceptor blocking activities were determined by reported procedures<sup>9,10</sup>.

The testing results are given in Table 1. Among the compounds tested, 7, 9, 13 and 15 were stimulants and 21 and 22 were depressants. No noteworthy  $\beta$ -adrenergic blocking activity was found in compounds 21, 22 and 28. Compounds 9 and 12 showed diuretic and anti-PCA activity respectively and compounds 15 and 21 exhibited antiinflammatory activity, which decreased at higher doses. However, none of them warrant further pursuit. The 4-hydroxy-4-phenylpiperidyl and 4-phenylpiperidienyl compounds (16-19) exhibited antiarrhythmic activity.

Regarding other biological activities, compounds 4 and 5 were tested for antimalarial activity by the method of Thurston<sup>11</sup>, in which both were found inactive at 150 mg/kg dose in mice.

The structures of the compounds were checked by IR spectra recorded on a Perkin-Elmer 157 spectrophotometer, PMR spectra on Varian EM-360L and Perkin-Elmer R-32 instruments (chemical shifts in  $\delta$ -scale downfield from TMS as internal standard) and mass spectra on a Jeol-JMS D-300 spectrometer. Purity of compounds was checked on silica gel G-plates and spots were located by iodine vapours or KMnO<sub>4</sub> spray. Melting points were taken in an electrically heated instrument and are uncorrected.

The spectral data of the compounds were found similar to those described in illustrative examples. The



SCHEME 1

experimental details are similar to those described in our earlier paper<sup>3</sup>.

*p*-(Cyclopent-1-enyl)phenol (3) was prepared by demethylation of *p*-(cyclopent-1-enyl)anisole (2)<sup>12</sup> with pyridine-HCl.

#### 4-(Cyclopent-2-en-1-yl)-2-(*N,N*-dimethylaminomethyl)phenol (4)

A solution of 1 (0.9 g, 5.6 mmol), dimethylamine (0.63 ml, 5.6 mmol), formaldehyde (0.42 ml, 5.6 mmol) and one drop of HCl in EtOH (50 ml) was refluxed for 12 hr, solvent distilled off and the residue taken up in C<sub>6</sub>H<sub>6</sub> (20 ml). The extract was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield 4 as an oil (0.8 g, 65%); PMR(CDCl<sub>3</sub>): 2.2 [*s*, 6H, N(CH<sub>3</sub>)<sub>2</sub>], 3.5 [*s*, 2H, ArCH<sub>2</sub>N], 3.7 [*h*, 1H, C-pentenyl C<sub>1</sub>-H], 5.75 [*m*, 2H, C-pentenyl C<sub>2</sub>-H and C<sub>3</sub>-H].

In a similar way compounds 5 and 7 were prepared. Their spectral data are as follows:

5—PMR(CCl<sub>4</sub>): 1.02 [*t*, 6H, (—CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, *J* = 7 Hz]; MS: *m/z* 245 (M<sup>+</sup>), 230 (M<sup>+</sup>—CH<sub>3</sub>), 173 (C<sub>12</sub>H<sub>13</sub>O), 72 (C<sub>4</sub>H<sub>10</sub>N), 48.

7—PMR(CDCl<sub>3</sub>): 2.26 [*s*, 3H, *o*-CH<sub>3</sub>—C<sub>6</sub>H<sub>4</sub>], 2.2-3.2 [*m*, 14H, (N<CH<sub>2</sub>)<sub>2</sub>], C-pentenyl 3-CH<sub>2</sub>, 4-CH<sub>2</sub> and 5-CH<sub>2</sub>], 3.75 [*h*, 3H, Ar—CH<sub>2</sub>N, OH], 6.0 [*m*, 1H, C-pentenyl C<sub>2</sub>-H], 6.6-7.3 [*m*, 7H, Ar—H].

#### 1-(Cyclopent-2-en-1-yl)-3-diethylamino-methyl-4-phenylcarbamoyloxybenzene (6)

A solution of 5 (0.2 g, 0.81 mmol) and phenyl isocyanate (0.1 g, 0.84 mmol) in pyridine (10 ml) was refluxed for 4 hr, concentrated, the residue taken up in C<sub>6</sub>H<sub>6</sub> and worked-up to get 6 as an oil (0.2 g, 67%); IR(neat): 1640 cm<sup>-1</sup> (CONH); PMR(CDCl<sub>3</sub>): 3.7 [*h*, 1H, C-pentenyl C<sub>1</sub>-H], 5.7 [*m*, 2H, C-pentenyl C<sub>2</sub>-H and C<sub>3</sub>-H].

#### 1-[*p*-(Cyclopent-2-en-1-yl)phenoxy]-3-(*N*<sup>4</sup>-phenylpiperazinyl)propane (15)

The reaction of 8 (1.1 g, 4.6 mmol) with *N*-phenylpiperazine (0.81 g, 5.0 mmol) in the presence of anhyd. K<sub>2</sub>CO<sub>3</sub> (1.35 g, 9.6 mmol) and NaI (0.69 g, 4.6 mmol) in dry acetone (40 ml) yielded 15 (0.95 g, 56%), m.p. 75-76°; PMR(CDCl<sub>3</sub>): 3.1 [*m*, 4H, N(CH<sub>2</sub>)<sub>2</sub>], 3.75 [*h*, 1H, C-pentenyl C<sub>1</sub>-H], 3.9 [*t*, 2H, OCH<sub>2</sub>, *J* = 6 Hz]; MS: *m/z* 362 (M<sup>+</sup>), 175 (C<sub>11</sub>H<sub>12</sub>N).

3-Chloro-1-[*p*-(cyclopent-2-en-1-yl)phenoxy]propane (8), 1,3-bis[*p*-(cyclopent-2-en-1-yl)phenoxy]propane (9), ethyl α-[*p*-(cyclopent-1-enyl)phenoxy]acetate (10), 3-[*p*-(cyclopent-1-enyl)phenoxy]prop-1-ene (11), 3-chloro-1-[*p*-(cyclopent-1-enyl)phenoxy]propane (12), 3-[*p*-(cyclopent-1-enyl)phenoxy]propionitrile (13), 1-[*p*-(cyclopent-1/2-en-1-yl)phenoxy]-3-(4-hydroxy-4-

Table 1—Physical and Pharmacological Data of Cyclopent-1/2-enylphenol Derivatives

Compd	Z N Z	R	Yield (%)	m.p. <sup>a</sup> C	Mol. formula	Analysis (%)		MS <i>m/z</i> (% intensity)	Pharmacological activities	
						Found	Calc.		<i>ALD</i> <sub>50</sub> (mg/kg)	Biological activities
4	NMe <sub>2</sub>	H	65	Oil	C <sub>14</sub> H <sub>19</sub> NO	N 6.7	6.4	—	—	—
5	NEt <sub>2</sub>	H	50	Oil	C <sub>16</sub> H <sub>23</sub> NO	N 5.5	5.7	245 (M <sup>+</sup> , 97), 173 (C <sub>12</sub> H <sub>13</sub> O, 100)	—	—
6	NHPh	CONHPh	67	Oil	C <sub>23</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub>	N 7.4	7.7	—	—	—
7	—	—	43	Oil	C <sub>23</sub> H <sub>28</sub> N <sub>2</sub> O	N 7.8	8.0	—	316	Stimulant <sup>c</sup>
8	Cl	—	54	Oil	C <sub>14</sub> H <sub>17</sub> ClO	—	—	236, 238 (M <sup>+</sup> , 37), 159 (100)	—	—
9	<i>p</i> -(cyclopent-2-enyl)phenoxy (O) <sub>2</sub> Et	—	25	Oil	C <sub>25</sub> H <sub>28</sub> O <sub>2</sub>	—	—	360 (M <sup>+</sup> , 21.6), 159 (86), 67 (C <sub>5</sub> H <sub>7</sub> , 100)	> 1000	Stimulant
10	—	—	66	Oil	C <sub>15</sub> H <sub>18</sub> O <sub>3</sub>	—	—	240 (M <sup>+</sup> , 68.3), 180, (49), 159 (68), 107 (100)	—	Diuretic <sup>d</sup> 88 AA <sup>e</sup> 25 ↓ 30 ↓ (1 × 10 <sup>-5</sup> g/ml)
11	(H = CH <sub>2</sub> )	—	64	Oil	C <sub>14</sub> H <sub>16</sub> O	C 83.7 H 7.9	84.0 8.0	—	—	AA 10 ↓ Weak hypotensive
12	CH <sub>2</sub> CH <sub>2</sub> Cl	—	67	84-86	C <sub>14</sub> H <sub>17</sub> ClO	—	—	236 (31.8), 238 (M <sup>+</sup> , 62.8), 132 (51), 94 (100), 41 (52)	—	AA 10 ↓ (1 × 10 <sup>-5</sup> g/ml) PCA <sup>f</sup> 63
13	CH <sub>2</sub> CN	—	60	128-30	C <sub>14</sub> H <sub>15</sub> NO	N 6.8	6.6	213 (M <sup>+</sup> , 100), 186 (36), 159 (41), 143 (51)	> 1000	Stimulant
14	N <sup>+</sup> -PhenylpiperazinyI	OH	61	107-09	C <sub>24</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub>	C 76.5 H 7.7	76.2 7.9	378 (M <sup>+</sup> , 65), 175 (100)	—	AA 14 ↓
15	N <sup>+</sup> -PhenylpiperazinyI	H	56	75-76	C <sub>24</sub> H <sub>30</sub> N <sub>2</sub> O	C 79.1 H 8.2	79.6 8.3	362 (M <sup>+</sup> , 39.2), 175 (100)	> 1000	Stimulant AI <sup>g</sup> 40 Weak hypotensive
16	4-Hydroxy-4-phenylpiperidyl	H	65	115-16 <sup>3</sup>	C <sub>25</sub> H <sub>31</sub> NO <sub>2</sub>	N 3.55	3.7	377 (M <sup>+</sup> , 36.4), 359 (30), 218 (71.5), 190 (100), 172 (72)	316	AA 12.5 ↓
17	—	—	62	153-55	C <sub>25</sub> H <sub>31</sub> NO <sub>2</sub>	N 3.5	3.7	377 (M <sup>+</sup> , 42.5), 190 (100), 172 (67.8)	—	AA 20 (1 × 10 <sup>-5</sup> g/ml)
18	—	—	78	70-72	C <sub>25</sub> H <sub>29</sub> NO	N 3.7	3.9	359 (M <sup>+</sup> , 28), 172 (100), 158 (95)	—	AA 20 ↓ 25 ↓ (1 × 10 <sup>-5</sup> g/ml)
19	4-Phenylpiperidienyl	H	68	64-65	C <sub>25</sub> H <sub>29</sub> NO	N 4.3	3.9	359 (M <sup>+</sup> , 40.7), 172 (100), 158 (84)	—	—
20	—	—	66	60-62	C <sub>14</sub> H <sub>16</sub> O <sub>2</sub>	—	—	216 (M <sup>+</sup> , 30), 159 (72), 57 (100)	—	—
21	NHCMe <sub>2</sub>	H	78	Oil	C <sub>17</sub> H <sub>25</sub> NO <sub>2</sub>	N 4.9	5.1	—	316	Depressant AI 38

Contd.

Table I—Physical and Pharmacological Data of Cyclopent-1/2-enylphenol Derivatives—Contd.

Compd	Z.N	R	Yield (%)	m.p. <sup>a</sup> °C	Mol. formula	Analysis (%)		MS <i>m/z</i> (% intensity)	Pharmacological activities	
						Found	Calc.		<i>ALD</i> <sub>50</sub> (mg/kg)	Biological activities
22	NHMe <sub>3</sub>	H	77	Oil	C <sub>18</sub> H <sub>27</sub> NO <sub>2</sub>	N 4.6	4.8	—	> 1000	Depressant AA 25↓ (1 × 10 <sup>-5</sup> g/ml)
23	NEt <sub>2</sub>	H	71	Oil	C <sub>18</sub> H <sub>27</sub> NO <sub>2</sub>	N 4.7	4.8	289 (M <sup>+</sup> , 14), 86 (96), 58 (100)	—	—
24	4-Hydroxy-4-phenylpiperidyl	H	58	104-6	C <sub>25</sub> H <sub>31</sub> NO <sub>3</sub>	N 3.1	3.5	—	—	—
25	N <sup>4</sup> -Phenylpiperazinyl	H	57	109-11	C <sub>24</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub>	N 7.1	7.4	378 (M <sup>+</sup> , 12.9), 175 (100)	464	—
26	N(Ac)CHMe <sub>2</sub>	Ac	76	Oil	C <sub>21</sub> H <sub>29</sub> NO <sub>4</sub>	N 4.05	3.9	359 (M <sup>+</sup> , 46.5), 43 (100)	—	—
28	NHMe <sub>3</sub>	H	74	65-67	C <sub>16</sub> H <sub>23</sub> NO <sub>3</sub>	N 5.4	5.05	277 (M <sup>+</sup> , 56.4) 72 (100)	—	Weak hypotensive

<sup>a</sup>(i) Oily compounds were purified by column chromatography over silica gel or alumina.

(ii) Superscript on m.p. refers to reference No. 3.

<sup>b</sup>Those analytical data which were found different than ±0.5% on repeated analyses are not included in Table and in lieu of this PMR data of such compounds are given below:

8—(CDCl<sub>3</sub>): 3.65 (*t*, 2H, CH<sub>2</sub>Cl, *J* = 6 Hz), 3.7 (*h*, 1H, C-pentenyl C<sub>1</sub>—H), 4.0 (*t*, 2H, OCH<sub>2</sub>, *J* = 6 Hz), 5.74 (*m*, 2H, C-pentenyl C<sub>2</sub>—H and C<sub>3</sub>—H).

9—(CCl<sub>4</sub>): 1.5 (*m*, 2H, C-pentenyl C<sub>4</sub>—H and C<sub>5</sub>—H), 2.0-2.5 (*m*, 8H, C-pentenyl C<sub>4</sub>—H<sub>2</sub>, C<sub>4</sub>—H<sub>2</sub>, C<sub>5</sub>—H, C<sub>5</sub>—H and OCH<sub>2</sub>CH<sub>2</sub>), 3.75 (*h*, 2H, C-pentenyl C<sub>1</sub>—H and C<sub>1</sub>—H), 4.02 [*t*, 4H, (OCH<sub>2</sub>)<sub>2</sub>, *J* = 7 Hz], 5.75 (*m*, 4H, C-pentenyl C<sub>2</sub>—H, C<sub>3</sub>—H, C<sub>3</sub>—H and C<sub>3</sub>—H), 6.7 (*dd*, 4H, Ar—H, *o*- to OCH<sub>2</sub>, *J* = 8 and 2 Hz), 6.95 (*dd*, 4H, ArH, *m*- to OCH<sub>2</sub>, *J* = 8 and 2 Hz).

10—(CDCl<sub>3</sub>): 1.2 (*t*, 3H, CH<sub>2</sub>CH<sub>3</sub>, *J* = 7 Hz), 4.0 (*q*, 2H, CH<sub>2</sub>—CH<sub>3</sub>, *J* = 7 Hz), 4.5 (*s*, 2H, OCH<sub>2</sub>), 6.0 (*t*, 1H, C-pentenyl C<sub>2</sub>—H, *J* = 2 Hz).

12—(CDCl<sub>3</sub>): 3.6 (*t*, 2H, CH<sub>2</sub>Cl, *J* = 6 Hz), 3.95 (*t*, 2H, OCH<sub>2</sub>, *J* = 6 Hz), 5.9 (*t*, 1H, C-pentenyl C<sub>2</sub>—H, *J* = 2 Hz).

20—(CDCl<sub>3</sub>): 2.75 (*m*, 2H, C—CH<sub>2</sub>), 3.2 (*m*, 1H, CH—CH<sub>2</sub>), 3.9 (*dd*, 1H, OCH, *J*<sub>gem</sub> = 12 Hz and *J*<sub>vic</sub> = 5.5 Hz), 4.15 (*dd*, 1H, OCH, *J*<sub>gem</sub> = 12 Hz, *J*<sub>vic</sub> = 3.5 Hz), 6.0 (*t*, 1H, C-pentenyl C<sub>2</sub>—H, *J* = 2 Hz).

<sup>c</sup>Depressant implies reduced spontaneous motor activity, ataxia, loss of righting reflex and stimulant implies alertness, straub phenomenon, excitement, hyper reflexia, preconvulsiveness and convulsions at 0.2 *ALD*<sub>50</sub> dose.

<sup>d</sup>The activity was studied in rats, figures denote percent fall of urine vol. at 0.2 *ALD*<sub>50</sub> dose against the value of 100 for chlorthiazide.

<sup>e</sup>AA = Antiarrhythmic activity on isolated guinea pig auricle. Figures denote the percentage decrease in maximal driving frequency at a concentration of 3 × 10<sup>-6</sup> g/ml.

<sup>f</sup>PCA = Passive cutaneous anaphylaxis, figures denote percent inhibition.

<sup>g</sup>AI = Antiinflammatory activity. Numbers denote the percent inhibition of carrageenin-induced Oedema in mice at 0.2 *ALD*<sub>50</sub> dose.

phenyl)piperidylpropanes (17 and 16), 1-(*p*-(cyclopent-2-en-1-yl)phenoxy]-3-(4-phenylpiperidienyl)propane (19), 1-[*p*-(cyclopent-1-enyl)phenoxy]-2,3-epoxypropane (20) and 3-substituted amino-1-(*p*-(cyclopent-1/2-en-1-yl)phenoxy/3-methylbenzofuran-4-yloxy)propan-2-ols (14, 21-26 and 28) were prepared by the methods described for respective analogs in our earlier paper<sup>3</sup> and their PMR spectra were found similar to those of the corresponding analogs. Their other physical and pharmacological data are given in Table 1.

Authors are thankful to Dr N Anand, Director and Dr S P Popli, Head, Medicinal Chemistry Division, CDRI, for encouragement and interest in this work and to Dr B N Dhawan, Head, Pharmacology Division and Dr A B Sen, Head, Parasitology Division for providing the biological data. Thanks are also due to Mrs K Bhutani, Mrs U Sharma and Amarnath for technical assistance.

## References

- (a) Kaiser J, Härtfelder G, Linder E & Schölkens B, *Arzneim Forsch*, **30** (1980) 420.  
(b) Kaiser J, *Arzneim Forsch*, **30** (1980) 427.  
(c) Vierhapper H, Dudczak R & Weldhaust W, *Arzneim Forsch*, **30** (1980) 1008.
- Rusching S, Schmitt K, Lessenich H & Härtfelder G, *Chem Abstr*, **72** (1970) 90054j.
- Kumar S & Rastogi S N, *Indian J Chem*, **22B** (1983) 659.
- Kar K, Rastogi S N, Starling S K & Dhawan B N, *Indian J Heart Res*, **1** Supp 1 (1980) 1.
- Alfred R Bader, *J Am chem Soc*, **75** (1953) 5967.
- Horn H J, *Biomedicine*, **12** (1956) 311.
- Dawes G S, *British J Pharmac*, **1** (1946) 90.
- Kar K, Mahanta P K, Popli S P & Dhawan B N, *Plantamedica*, **42** (1981) 75.
- Srimal R C & Dhawan B N, *J Pharma Pharmac*, **25** (1973) 447.
- Jain P C, Belleau B, Rastogi S N, Anand N, Tripathi O N & Srimal R C, *Indian J Chem*, **12** (1974) 1021.
- Thurston J P, *Brit J Pharma Chem*, **5** (1950) 409.
- Pascual V José & Crespo R, *Annals real Soc Espan*, **48B** (1952) 273.

## Chemistry of Carbenes: Part II— Reaction of Methylene with Dimethyl Ether

R K S MEHTA†

University of Edinburgh, Edinburgh, Scotland

Received 13 August 1984; revised 10 October 1984; accepted 16 May 1985

Relative rates of insertion of methylene into the primary C—H bonds of dimethyl ether have been determined from its competitive reactions with diethyl ether. At 100°C, the efficiency of attack on primary C—H bond of the former is 1.72 based on unity for that of the latter indicating marked selectivity of attack on primary C—H bond of dimethyl ether. Although acetaldehyde is found in the products it is considered unlikely to arise from abstraction reaction of methylene.

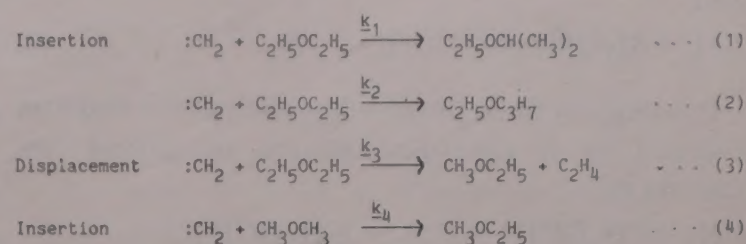
In an earlier communication<sup>1</sup>, methylene was shown to react with diethyl ether. In addition to insertion reaction into 1° C—H bond to give ethyl *n*-propyl ether, two novel reactions: displacement reaction in which it gave rise to a methyl alkyl ether and displaced an olefin; and a displacement reaction in which the biradical methylene behaved like a monoradical. The same insertion reaction of methylene with dimethyl ether is now found to give methyl ethyl ether. The present study is likely to provide information on selectivity of methylene towards 1° C—H bonds in different ethers. Competitive rate measurements of the insertion reaction of methylene into 1° C—H bonds of dimethyl and diethyl are therefore inevitable. Such an approach is dictated by the fact that the absolute concentration of methylene biradicals cannot be obtained. Many of the difficulties disappear when measurements of relative rates of attack on any two ethers R—O—R and R'—O—R' (by analogy, the competitive reactions of atom and free radicals with hydrocarbons) are carried out. These experiments with diethyl ether have already been reported<sup>1</sup> for the present study dimethyl ether has been chosen in order to keep a sequence of lower to higher ethers (to follow) in the discussions.

The apparatus and analytical equipment were the same as used before<sup>1</sup>. Mixtures of ketene and ether in the ratio 1:3 to 1:8, keeping the total pressure below 15 cm in the reaction vessel were irradiated to ~20% decomposition of ketene.

The insertion reaction of methylene with dimethyl ether gave rise to methyl ethyl ether indicating an

attack on the primary C—H bonds. The same reaction with diethyl ether gave ethyl *n*-propyl ether<sup>1</sup>.

In the presence of both dimethyl ether and diethyl ether, the following reactions occur (Scheme 1).



Scheme 1

Thus, methyl ethyl ether arises by reactions (3) and (4) from both the ethers. The Scheme 1 then gives the rate ratios:

$$R_{\text{MeOEt}}/R_{\text{EtOPr}^n} = k_3/k_2 + k_4/k_2 \frac{[\text{MeOMe}]}{[\text{EtOEt}]} \quad \dots (1)$$

The  $k_4/k_2$  values calculated as above are given in Table 1. The molar average is calculated to be 1.72 from the data on the competitive methylene insertion reactions with dimethyl and diethyl ethers given in Table 1. At 100°C, values for the left hand side of Eq. (1) are listed in Table 1, under column marked MeOEt. At corresponding temperature, values for  $k_3/k_2$  (the average rate ratio for MeOEt/EtOPr<sup>n</sup> formation from EtOEt alone) are found<sup>1</sup> to be 0.38. This has to be allowed for since the MeOEt also arises from EtOEt by a novel mode of reaction, i.e., displacement reaction. The ratios of the two ethers used are also given in Table 1. Substituting the values in the aforementioned relationship,  $k_4/k_2$  values were calculated and are given in Table 1. Their average comes to 1.72. Since there are six primary C—H bonds

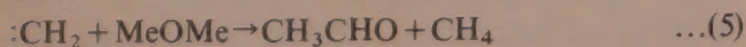
Table 1—Competitive Reactions of Methylene with Dimethyl and Diethyl Ethers

[Temp = 100°C; $k_3/k_4 = 0.38$ ]					
Pressure (cm)			Normalized to EtOPr <sup>n</sup>		
Ketene	MeOMe	EtOEt	MeOEt	EtOPr <sup>1</sup>	$k_4/k_2$ (Calc.)
1.0	4.1	4.0	2.07	1.58	1.65
1.0	8.0	4.6	3.16	1.91	1.60
2.0	8.0	4.0	3.77	1.76	1.69
1.0	4.0	2.0	3.85	1.64	1.74
2.0	8.0	4.0	4.24	1.77	1.93
0.5	3.0	1.0	5.48	1.79	1.70
*Molar average				1.74*	1.72*

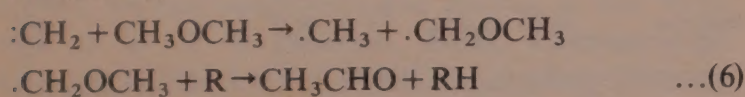
†Present address: Polymers Department, General Motors Research Laboratories, Warren, Michigan 48090-9055 (USA).

available in both MeOMe and EtOEt, the results show that the efficiency of attack on primary C-H bond of the former is higher than that of the latter. Acetaldehyde is also found in small quantities as the product of the reaction of  $\cdot\text{CH}_2$  with MeOMe but its formation has not been followed in detail.

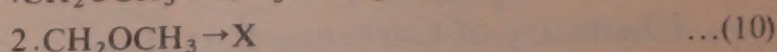
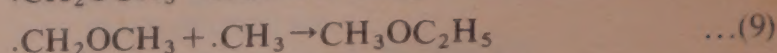
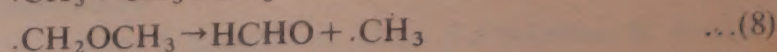
Acetaldehyde could be formed by way of direct molecular reaction via a somewhat complex transition state



It is unlikely to be the result of abstraction reaction followed by a disproportionation of radical (see reaction 6),



because a deep seated rearrangement of atoms would be required. Abstraction of hydrogen from MeOMe has of course been observed with methyl radicals<sup>2</sup> and at high temperatures (270-400°C) where the decomposition of  $\cdot\text{CH}_2\text{OCH}_3$  radical gives formaldehyde ( $\text{CH}_2\text{O}$ ). The reactions which take place are probably (7-10).



Reaction (5) has been studied by various workers<sup>2-4</sup>. Its activation energy has been shown to be 10 kcal.

For dimethyl ether, the value of 1.72 for the bond reactivity based on unity for the primary bond in diethyl ether indicates marked selectivity of attack on primary bond of dimethyl ether. The absence of lower hydrocarbons such as, ethane from methylene reaction with neat dimethyl ether confirms the expected lack of abstraction reaction involving  $\cdot\text{CH}_3$  formation followed by its dimerization.

## References

- 1 Mehta R K S, *Indian J Chem*, **24B** (1985) 1239.
- 2 Leermaker J, *J Am chem Soc*, **56** (1934) 1899.
- 3 Rice F U & Herzfeld, *J Am chem Soc*, **56** (1934) 284.
- 4 Marcus R A, Darwent B & Steacie E W R, *J chem Phys*, **16** (1948) 987.
- 5 Trotman-Dickenson A F & Steacie E W R, *J chem Phys*, **19** (1951) 329.

# CSIR SCIENTIFIC PERIODICALS

## JOURNAL OF SCIENTIFIC & INDUSTRIAL RESEARCH (Monthly)

With a fine record of over 45 years' service to the scientific community, this journal has grown into India's leading general science periodical. Intended to fulfil the responsibility of helping the research workers to keep themselves abreast of current developments in various fields of science and technology, the journal carries editorial features highlighting important scientific events in India and abroad, articles on science policy and management of science review articles on topics of current research interest, technical reports on international and national conferences, reviews of scientific and technical publications, and notes on major advances in various fields.

Annual subscription	Rs 120.00	\$ 40.00	£ 23.00
Single copy	12.00	4.00	2.30

## INDIAN JOURNAL OF CHEMISTRY (Monthly)

Section A: Started in the year 1963, the journal is devoted to papers in Inorganic, Physical, Theoretical and Analytical Chemistry.

Annual subscription	Rs 160.00	\$ 53.00	£ 30.00
Single copy	16.00	5.30	3.00

Section B: This journal is devoted to papers in Organic Chemistry, including Medicinal Chemistry.

Annual subscription	Rs 160.00	\$ 53.00	£ 30.00
Single copy	16.00	5.30	3.00

## INDIAN JOURNAL OF PURE & APPLIED PHYSICS (Monthly)

Started in the year 1963, this journal is devoted to original research communications (full papers and short communications) in all conventional branches of physics (except radio and space physics).

Annual subscription	Rs 180.00	\$ 60.00	£ 34.00
Single copy	18.00	6.00	3.40

## INDIAN JOURNAL OF RADIO & SPACE PHYSICS (Bimonthly)

The journal, which is being published beginning from March 1972, is intended to serve as a medium for the publication of the growing research output in various areas of radio and space physics, such as ionospheric propagation, magnetosphere, radio and radar astronomy, physics and chemistry of the ionosphere; neutral atmosphere; airglow, winds and motion in the upper atmosphere; stratosphere-mesosphere coupling, ionosphere-magnetosphere coupling; solar-terrestrial relationship, etc.

Annual subscription	Rs 100.00	\$ 34.00	£ 19.00
Single copy	20.00	6.80	3.80

## INDIAN JOURNAL OF TECHNOLOGY (INCLUDING ENGINEERING) (Monthly)

This journal publishes papers reporting results of original research of applied nature pertaining to unit operations, heat and mass transfer, products, processes, instruments and appliances, etc. The journal is of special interest to research workers in departments of applied sciences in universities, institutes of higher technology, commodity research laboratories, industrial cooperative research institutes, and industrial research laboratories.

Annual subscription	Rs 120.00	\$ 40.00	£ 23.00
Single copy	12.00	4.00	2.30

## INDIAN JOURNAL OF EXPERIMENTAL BIOLOGY (Monthly)

This journal, devoted to the publication of research communications in the fields of experimental botany, zoology,

microbiology, pharmacology, endocrinology, nutrition, etc., is the only one in India with such a wide coverage and scope.

Annual subscription	Rs 180.00	\$ 68.00	£ 34.00
Single copy	18.00	6.80	3.40

## INDIAN JOURNAL OF BIOCHEMISTRY & BIOPHYSICS (Bimonthly)

This journal, published in association with the Society of Biological Chemists (India), Bangalore, is the only research journal in India devoted exclusively to original research communications in biochemistry and biophysics.

Annual subscription	Rs 65.00	\$ 23.00	£ 12.00
Single copy	13.00	4.60	2.40

## INDIAN JOURNAL OF MARINE SCIENCES (Quarterly)

Commencing publication from June 1972, this journal is devoted to research communications (full papers and short communications) pertaining to various facets of marine research, viz. biological, physical, geological and chemical oceanography.

Annual subscription	Rs 90.00	\$ 30.00	£ 17.00
Single copy	26.00	8.70	5.00

## RESEARCH AND INDUSTRY (Quarterly)

Intended to serve as a link between science and industry, this journal is addressed primarily to technologists, engineers, executives and others in industry and trade. It publishes informative original articles containing practical details of processes and products devoted in India, which show promise of ready utilization, and technical digests on new processes, products, instruments and testing methods which are of interest to industry. Developments in Indian industry are regularly reported.

Annual subscription	Rs 70.00	\$ 23.00	£ 13.00
Single copy	22.00	7.00	4.00

## INDIAN JOURNAL OF TEXTILE RESEARCH (Quarterly)

Commencing publication from March 1976, this journal is devoted to the publication of papers reporting results of fundamental and applied researches in the field of textiles.

Annual subscription	Rs 50.00	\$ 17.00	£ 10.00
Single copy	15.00	5.00	3.00

## MEDICINAL & AROMATIC PLANTS ABSTRACTS (Bimonthly)

Carries informative abstracts of scientific papers published in important Indian and foreign journals relating to different aspects of medicinal and aromatic plants. Each issue contains about 350 abstracts with a subject index.

Annual subscription	Rs 120.00	\$ 40.00	£ 23.00
Single copy	24.00	8.00	4.60

## CURRENT LITERATURE ON SCIENCE OF SCIENCE (Monthly)

Carries abstracts, digests, book reviews, news & notes and R&D statistics with emphasis on problems of S&T in developing countries, it also covers the areas of science policy, R&D planning and management, technology transfer, technology assessment and science and society.

Annual subscription	Rs 100.00	\$ 30.00	£ 12.00
---------------------	-----------	----------	---------

Please contact

Manager (Sales & Advertisement)  
PUBLICATIONS & INFORMATION  
DIRECTORATE, CSIR  
Hillside Road, New Delhi-110012

# CSIR PUBLICATIONS

## WEALTH OF INDIA

*An encyclopaedia of the economic products and industrial resources of India issued in two series*

**RAW MATERIALS SERIES**—contains articles on plant, animal and mineral resources

	Rs	\$	£
Vol. I (A-B)	80.00	30.00	13.00
Vol. II (C)	95.00	33.00	17.00
Vol. III (D-E)	105.00	32.00	20.00
Vol. IV (F-G)	65.00	27.00	12.00
Supplement (Fish & Fisheries)	40.00	16.00	7.00
Vol. V (H-K)	114.00	34.00	21.00
Vol. VI (L-M)	90.00	34.00	15.00
Supplement (Livestock)	102.00	34.00	19.50
Vol. VII (N-Pe)	100.00	30.00	19.00
Vol. VIII (Ph-Re)	86.00	32.00	14.00
Vol. IX (Rh-So)	104.00	35.00	19.00
Vol. X (Sp-W)	225.00	75.00	42.50
Vol. XI (X-Z)	115.00	38.50	22.00

**INDUSTRIAL PRODUCTS SERIES**—deals with major, small-scale and cottage industries

Part I (A-B)	58.00	20.00	11.00
Part II (C)	74.00	24.00	14.00
Part III (D-E)	100.00	33.50	19.50
Part IV (F-H)	126.00	42.00	24.00
Part V (I-L)	30.00	9.00	3.00
Part VI (M-Pi)	28.00	8.00	2.80
Part VII (Pi-Sh)	60.00	18.00	6.00
Part VIII (Si-Ti)	66.00	27.00	10.00
Part IX (To-Z)	80.00	34.00	12.00

**BHARAT KI SAMPADA** (Hindi Edition of Wealth of India, Raw Materials):

Vol. I (अ-क)	38.00	16.00	6.50
Vol. II (क)	36.00	15.00	6.00
Vol. III (ख-न)	36.00	15.00	6.00
Vol. IV (प)	83.00	34.00	16.00
Vol. V (फ-ये)	60.00	22.00	10.00
Vol. VI (वे-ह)	80.00	27.00	13.00
Vol. VII (ह-वा)	135.00	40.00	25.00
Livestock (Kukkut Palan)	34.00	15.00	6.00
Fish & Fisheries (Matsya aur Matsyaki)	49.00	21.00	8.00
A Dictionary of Generic & Specific Names of Plants and Animals Useful to Man with their English and Latin pronunciation in Devanagari	30.00	11.00	5.00

## OTHER PUBLICATIONS

Proceedings: seminar on primary communications in Science & Technology in India by

Sh. R.N. Sharma & S. Seetharama	52.00	17.50	9.00
Flora of Delhi by J.K. Maheshwari	28.00	8.00	2.80
Indian Fossil Pteridophytes by K.R. Surange	66.00	22.00	12.50
Indian Thysanoptera by T.N. Ananthakrishnan	26.00	8.00	2.60
The Millipede Thyropygus by G. Krishnan	12.00	3.50	1.20
Drug Addiction with special reference to India by R.N. Chopra & I.C. Chopra	12.00	3.50	1.20
Glossary of Indian Medicinal Plants by R.N. Chopra & I.C. Chopra	35.00	13.00	6.00
Fluidization & Related Processes	12.00	4.00	1.20
Evolution of Life by M.S. Randhawa, A.K. Dey, Jagjit Singh & Vishnu Mitre	22.50	7.00	2.25
Collected Scientific Papers of Meghnad Saha	30.00	9.00	3.00
Proteaceae by C. Venkata Rao	72.00	24.00	13.50
Pinus by P. Maheshwari & R.N. Konar	30.00	11.00	5.00
Cellulose Research I	3.00	0.90	0.30
Cellulose Research II	6.00	1.75	0.60
Chemical Process Design	9.00	2.50	0.90
Low Temperature Carbonization of Non-coking Coals & Lignites & Briquetting Coal Fines:			
Vol. I & Vol. II (each volume)	17.50	5.50	1.75
Nucleic Acids	10.00	3.00	1.00
IGY Symposium: Vol. I	9.00	2.50	0.90
IGY Symposium: Vol. II	9.00	2.50	0.90
CNS Drugs	16.50	5.00	1.65
Kinetics of Electrode Processes & Null Points of Metals	2.50	0.75	0.25
Indian Sardines by R.V. Nair	22.00	7.00	2.20
Termite Problems in India	9.00	3.00	0.90
Loranthaceae by B.M. Johri & S.P. Bhatnagar	55.00	18.50	10.50
Abies and Picea by K.A. Chowdhury	14.00	6.00	2.10
Gnetum by P. Maheshwari and Vimla Vasil	20.00	6.00	2.00
Aquatic Angiosperms by K. Subramanyam	20.00	6.00	2.00
Supplement to Glossary of Indian Medicinal Plants by R.N. Chopra, I.C. Chopra & B.S. Varma	18.00	7.00	3.00
Herbaceous Flora of Dehra Dun by C.R. Babu	144.00	60.00	22.00
Diosgenin and Other Steroid Drug Precursors by Y.R. Chadha & Miss L.V. Asolkar	36.00	13.00	6.00
Research & Development Management by Inder Dev	25.00	10.00	—
Rural Development and Technology—A Status Report-cum Bibliography by P.R. Bose & V.N. Vashist	100.00	38.00	17.00
Cholera Bacteriophages by Sachimohan Mukherjee	30.00	10.00	6.00

Packing and Postage extra

Please contact:

Manager (Sales & Advertisement)

**PUBLICATIONS & INFORMATION DIRECTORATE, CSIR**  
Hillside Road, New Delhi 110012

Printed & Published by Shri S.S. Saksena, Editor, Publications & Information Directorate (PID)  
Hillside Road, New Delhi 110012, at PID Photocomposition-cum-Printing Unit

Regd No. D(C)-1018